Drug Addiction and the U.S. Public Health Service

National Institute on Drug Abuse
U.S. Department of Health, Education, and Welfare
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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Drug Addiction and the U.S. Public Health Service

Proceedings of Symposium Commemorating the 40th Anniversary of the Addiction Research Center at Lexington, Ky.

Edited by
William R. Martin, M.D., M.S., and Harris Isbell, M.D.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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Dr. Lawrence C. Kolb, Sr. *(1881–1972), Medical Officer in Charge, U.S. Public Health Service Hospital, Lexington, 1935–38*

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Foreword

In 1929 Congress authorized the establishment of two narcotic hospitals, which came to be located in Lexington, Kentucky, and Ft. Worth, Texas. The Lexington facility was the first to open; however, before its opening in 1935, Dr. C. K. Himmelsbach initiated studies on narcotic addiction in man in 1933 in the U.S. Prison Annex at Leavenworth, Kansas. For many years, the two hospitals were the only places in the Nation providing treatment for drug-dependent individuals. They also became the primary international centers of learning and expertise about addiction processes.

The Addiction Research Center (ARC) has played a unique and historic role over the last 40 years. It has been the cradle of treatment and research in the drug abuse field. Until the last decade, it stood almost alone. In the last few years, the harvest of the ARC has been reaped not only in the United States but throughout the world. The knowledge base we now depend on can be traced to the ARC's solid scientific work during the last four decades. Many of the people who are now leaders in the drug abuse and mental health fields were trained at Lexington. In this volume, these fabulous 40 years are reviewed. This book will be of interest to workers and researchers in the drug abuse and related biomedical fields, and to historians of science. It tells a noble story of a quest for basic understanding of one of the most important and difficult issues of our time, drug abuse.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

Preface

This volume will serve several purposes. It may recall for the participants 3 very pleasant days (June 9–11, 1975) when a number of the innovators who established the drug abuse programs of the U.S. Public Health Service, as well as friends and longtime associates of the program, met with current and former staff members of the two U.S. Public Health Service narcotic hospitals and the Addiction Research Center. It was our hope that the symposium and this volume would also give a historical account of the development of the Federal drug abuse programs.

While joyed by seeing old friends and colleagues, those attending the symposium were saddened by the absence of those who had passed on, including Lawrence Kolb, Sr., Walter Treadway, W. F. Ossenfort, J. K. Fuller, J. D. Reichard, Nathan B. Eddy, and Anna Eisenman. Also missing for reasons of health were Mike Pescor, H. K. Beecher, since deceased, M. H. Seevers, and Harris Hill. Karl Frank was abroad and could not attend.

The idea of having a meeting to commemorate the 40th anniversary (1935–1975) of the Addiction Research Center was that of Dr. C. K. Himmelsbach. It was strongly endorsed by the staff of the Addiction Research Center as well as by Drs. Isbell, Wikler, and Fraser. We felt that the 40th anniversary would be a unique time to recall how the present endeavor started, as well as to review the accomplishments of the program, a sentiment which we felt Dr. Himmelsbach shared. The 40th anniversary occurred approximately a year following transfer of the Lexington Clinical Research Center to the Bureau of Prisons, at a time when there were indications that the program of the Addiction Research Center would also change.

We were exceptionally fortunate to have Dr. Maddux prepare a paper recounting the history of the two hospitals and Dr. Rasor to tell of the problems associated with changing the mission of a large and well-established institution and to have them put these two remarkable institutions into perspective. Shortly after the Lexington Clinical Research Center was transferred to the Bureau of Prisons, a close and longtime associate of the program commented that he knew if he stayed around long enough, Lexington would end up the way it started, thus expressing the cyclic nature of both institutional evolution and scientific thinking.

Several of the papers and round tables represent edited extemporaneous remarks. In some ways they may be the most valuable of the contributions for they describe views and problems as they were formulated by both scientists and administrators at the times events were happening. Day-to-day decisions, whether they had narrow or broad implications, were frequently made on the basis of the most practical and immediate considerations. The reader of the volume may thus have a better understanding of the history of the efforts of the U.S. Public Health Service to cope with the problem of drug addiction. Although some of the authors edited out some of their more harsh statements which reflected irritations that have remained fresh despite the passage of time, we are impressed that events, as we have known them, have been described forthrightly.

It is appropriate that some comments be made about the relationship between the Lexington Hospital and the Addiction Research Center. The relationship between the U.S. Public Health Service Hospital at Lexington and the Addiction Research Center extended over the life of the hospital and to our knowledge was good—not optimal—but good. In retrospect, both research and the hospital could have given more to each other. However, in the end, clinicians and administrators who have the responsibilities for managing and treating patients only rarely are equipped to conduct research or have faith that research will eventually solve problems. On the other hand, the scientist, who at any given time may have nothing to offer either patients or clinicians, may have an abiding faith that a disease process will yield to efforts but have little sympathy for the therapist whose ministrations are at best marginally effective. It is our opinion that it is important that medical researchers (at least some) have contact with sick patients and their pathology if for no other reason than that it will help dispel delusions about the disease. The Lexington Hospital and the Addiction Research Center together were more effective than the sum of their individual efforts. The intramural research program of the National Institute on Drug Abuse should have a close relationship with an intramural research-oriented treatment facility.

The Addiction Research Center has had a continuing relationship with the National Research Council's Committee on Problems of Drug Dependence for over 40 years. The Addiction Research Center has also had a continuing relationship with the World Health Organization for many years. It is appropriate that Drs. May and Cameron, who have played significant roles in these organizations, should discuss their activities.

The educational activities of the hospitals and the Addiction Research Center have been extensive and were not adequately covered in the papers presented. The editors must accept the responsibility for this omission.

Originally the Division of Mental Hygiene trained young physicians as psychiatrists by affiliation with the Department of Psychiatry of the University of Colorado School of Medicine. Those sent for training were commissioned officers who were serving in the medical service of the Federal Prison System or in the Lexington and Fort Worth Hospitals. After training at Colorado, these young men returned to the Public Health Service in various capacities. They became staff psychiatrists. They set up and operated psychiatric residency programs. Some rose to prominence in mental health administration. The roster of those who went through the program reads almost like a Who's Who. Included are Robert Felix, Mike Pescor, Victor Vogel, Dale Cameron, Jim Lowry, Robert Rasor, and Murray Diamond.

These people became responsible for the psychiatric residency programs which were conducted in both the Lexington and Fort Worth Hospitals. The programs trained many psychiatrists, some of whom remained in the Public Health Service, while some went on to fields outside the Service. Some of those who went through the residency programs included Abraham Wikler, Fred Maddux, and Warren Jurgensen. Many of those who went into private practice found themselves sought after as authorities with expertise in drug dependence.

The Addiction Research Center cooperated with many medical schools in teaching undergraduate medical students the facts of drug dependence. All senior members of the Addiction Research Center were involved. Lectures and movie demonstrations were given at 15 to 20 medical schools annually, including the Universities of Illinois, Michigan, Cincinnati, Louisville, Rochester, Columbia, Cornell, Dartmouth, Virginia, Iowa, Vanderbilt, Kentucky, Stanford, Buffalo, Arkansas, Maryland, and Emory. These activities not only provided instruction for about 1,500 medical students annually but also were one means of interesting and recruiting personnel. Bill Martin and Don Jasinski were recruited through these activities.

Relationships with the universities also led young graduate students and investigators to come to the Addiction Research Center to study and conduct research. Some of the people who worked with us include Raymond Houde, Joe Cochin, Conan Kornetsky, Dick Belleville, Bruce Vaupel, Charles Haertzen, Paul Gilbert, Masako Nozaki, James Bell, Terry Christian, Salvatore Mulé, Carter Carr, Wallace Pickworth, Lawrence Sharpe, and Jeffrey Pevnick; all of whom have made very substantial contributions.

The advent of the program of permitting young physicians to fulfill their military obligation by serving 2 years in the Public Health Service added another source of fine personnel. Among those who did their

2-year stint with us were Al Wolbach, Charles Gorodetzky, David Rosenberg, T. K. McClane, Donald Jasinski, Joseph Sapira, Peter Mansky, and Jay Nutt.

This volume tells how a group of able and dedicated Government employees dealt with problems of drug addiction and legislative mandates. This has been a time when the public's frustrations with problems of drug addiction have been reflected in changing laws, which varied in the degree and extent to which illicit and pathologic drug use was punished, and in the relative roles of research and treatment. It is obvious that neither scientists, therapists, nor enforcement people have met the public's expectations. It also is obvious that our commonsense formulations of the addiction process and its treatment have not been adequate. Humane and efficacious treatments of addiction processes will in all probability await a definitive and mechanistic formulation of the disease process.

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Psychiatric, Psychological, and Epidemiological Aspects of Drug Dependence: Status Prior to 1944

Robert H. Felix, M.D., M.P.H.

It is an interesting fact that 1975 marks not only the 40th year since the establishment of the Research Program at the Lexington Hospital but the 50th year since the publication of a series of papers which have come to be regarded as classics in the field of drug addiction and which established as the preeminent authority in the behavioral aspects of the problem the man who led us and developed our interest in the problem. The three landmark papers of Lawrence Kolb were published in 1925: "Drug addiction in its relation to crime" [9] in January, "Types and characteristics of drug addicts" [10]in April, and "Pleasure and deterioration from narcotic addiction" [11] in October. Certainly the work carried on by psychiatrists, psychologists, and other behavioral scientists at Lexington from 1935 to 1944 and for a long time afterward stemmed from these papers either directly or indirectly. With the support and assistance given by the Chief of the Division of Mental Hygiene, Dr. Walter L. Treadway, himself one of the Nation's leading psychiatrists, and the scientific leadership of Dr. Kolb, the research effort here, prior to 1945, could be matched at no other station of the Public Health Service except the National Institutes of Health; and the quality and quantity of research in behavioral sciences could be matched nowhere in the Public Health Service.

While the advances in our knowledge of the psychological factors operating in the etiology of drug addiction have been great since Kolb published his classical papers, the relevant literature goes back at least to 1874. In that year, Stille [18] wrote of the need of some individuals to use opium to promote agreeable thoughts, Jouet [8], Pepper [13], and Schmidt [17] spoke of the seductive psychic effects of opium. Wilson and Eshner [19], before the turn of the century, reported a tendency for emotionally unstable people to resort to opiates, and considered pain—mental as well as physical—as the principal etiologic factor in beginning and continuing morphine use. Rhein [16] considered all or at least most addicts as psychopathic personalities by which he meant individuals "who have not adjusted (themselves) to (their) emotional reactions." Claude [2] divided addicts into two categories: constitutional and accidental. He considered the former as having a "constitutional predisposition" to the use of drugs. This constitutional predisposition is psychological in nature and is manifested by a "deliberate and intense search for abnormal, unusual, or mysterious states."

In 1923 Kolb began his studies of narcotic addiction at the Hygienic Laboratories which resulted in a series of papers including those referred to above. Dr. Kolb had been interested in the problem of alcoholism and drug abuse since 1914 when the Service had assigned him to immigration duty at Ellis Island, N.Y. His studies led him to conclusions which were at variance with the commonly held notion both of physicians and laymen concerning the psychological effect of opiates on humans. The addict was commonly called a "fiend" by the lay public and was regarded in that light while such serious investigators as Dupouy [4, 5], deFursac and Rosanoff [3], Bell [1], and Gelma [7] among others, used the term "morphinomania" in describing addiction. DeFursac and Rosanoff, in fact, speak of the "morphinomaniacs" as "degenerates" and Bell defines the morphinomaniac as one who takes morphine "for pleasure or as a stimulant and in ever increasing doses."

Kolb in studying the role of pleasure in producing addicts differentiates between two kinds of pleasure. In his paper on pleasure and deterioration [11] he sets forth his concept most clearly in the following words:

"Relief from pain, long-continued distress, or unusual anxiety, no matter by what means accomplished, is accompanied by a pleasant relaxation and a sense of ease. When the distress has been great and relief sudden, a short period of happiness may ensue, during which the world seems more beautiful than ever before and one wonders why trifling inconveniences should ever cause discontent. Feelings somewhat akin to the above may sometimes be produced by opium in normal persons who are relieved from intense suffering by it. But in referring to the mental pleasure of opium, a distinction should be made between the pleasure that is merely a reflex following relief from anxiety and pain and the pleasure that results from raising an individual above his usual emotional plane. . . . studies. . . seem to show that normal as well as abnormal persons may receive the first kind of pleasure, while only in rare instances, if at all, does anyone except the emotionally unstable, the psychopath, or the neurotic receive the latter. The first, a reflex from relief of conditions that are temporary and accidental, may be termed *negative* pleasure; the second, a relief from conditions that are more or less permanent or fundamental, may be termed *positive* pleasure.

"In persons who at first receive *positive* pleasure from an opiate and because of it continue the use of the drug until it becomes a physical necessity, the degree of the feeling wanes as more and more of the drug becomes necessary to satisfy the craving of physical addiction and to maintain comfort. . . . As tolerance to larger and larger doses of opiates is established, positive pleasure is decreased or is not aroused at all. . . . Amounts that at first gave unusual effects are then necessary to maintain what to an addict is normal functioning and to ward off discomfort. . . . It thus happens that the drug, taken in the beginning because of its power to raise an inferior individual above his normal level, must be taken in the end to keep him from sinking below it and to relieve conditions that the drug itself has produced.

"After the first stage of addiction, the motive for it is not pleasure, but the avoidance of pain. . . ."

Consistent with his concept of the psychologically calming and soothing effect of opium, Kolb sharply differed with those who maintained that one effect of these substances was to inflame the addict to commit criminal acts.

In the first of these papers published in 1925, "Drug addiction in its relation to crime," he stated that "there is probably no more absurd fallacy extant than the notion that murders are committed and daylight robberies and holdups are carried out by men stimulated by large doses of heroin or cocaine which have temporarily distorted them into self-imagined heroes incapable of fear.

". . . addiction to opium or any of its preparations creates two tendencies directly opposed to each other. The immediate effect of excessive indulgence in all forms of the drug is to soothe abnormal impulses, while the ultimate effect is to create a state of idleness and dependency which naturally enhances the desire to live at the expense of others and by antisocial means. The effect of addiction on the psychopathic murderer is to inhibit his impulse to violent crime. At the same time it saps his vitality and reduces the ambition and courage that prompt him to convert his abnormal impulse into action. . . . The factor most important in this is the desire to secure the drug in order to avoid the discomfort caused by the lack of it. No addict who receives an adequate supply of opium and has money enough to live is converted into a liar or thief by the direct effect of the drug itself. The direct effect is to remove the irritability and unrest so characteristic of psychopathic individuals.

* * * * *

"The mental and physical lethargy and the loss of ambition produced by morphine and heroin are incompatible with the simultaneous production of an aggressive hero."

Perhaps the most succinct description of the psychological effects of opium derivatives is the following, taken from the same paper:

"One of the effects of opium is the obliteration of mental conflicts and of the uncomfortable pathological strivings that result from them. The tensions, both physical and mental, produced by these strivings are relieved, and under its influence the neurotic or psychopathic patient feels free, easy, and contented. The contrast with his usual state is so great in some cases that he is actually happy. The condition may be expressed in another way by saying that the patient has sublimated his pathological impulses by the use of a narcotic. The objection to this form of sublimation is that it is itself temporary and pathological. The reflex from waning narcotism accentuates the original tensions, just as release from these tensions accentuates the pleasure of narcotics beyond normal expectations, and in the end the patient is worse off. The depression that so often follows the withdrawal of opium is in part explained in this way. . . . In nearly every instance where the drug has been taken in large quantities by a morose, irritable, restless, discontented individual, the inflation for the time being has made him agreeable, pleasant, and nonaggressive. It is, in fact, the pleasant satisfaction with things as they are that causes addicts to lose ambition and willpower. Addiction to opium will not prevent criminals from committing violent crimes—the inflation is too temporary to bring about such a good result, and when tolerance is established, the effect is diminished in intensity . . . the effect on an aggressive criminal is to make him less a murderer and more a thief . . . when his personality is inflated. Everything is satisfactory and nothing matters."

To many of those who looked to him as their mentor, Kolb's most significant paper on the psychological and social aspects of addiction was the report of his studies on 230 cases, also published in 1925 [10]. This paper set forth his classification of addicts which was the basis for subsequent studies by Pescor [14], Felix [6], and others who were associated with him during the early days of the Research Center and the hospital. There were five categories described in this paper as follows:

1. People of normal nervous constitution accidentally or necessarily addicted through medication in the course of illness.
2. Care-free individuals, devoted to pleasure, seeking new excitements and sensations, and usually having some ill-defined instability of personality that often expresses itself in mild infractions of social customs.
3. Cases with definite neuroses not falling into classes 2, 4, or 5.
4. Habitual criminals, always psychopathic.
5. Inebriates.

In 1938, Kolb and Ossenfort [12] added a sixth category, "Drug addicts with associated psychosis."

Group 1, individuals with "normal nervous make-up" constituted 14 percent of the cases studied. It was noted that if those who were given opiates for legitimate reasons were excluded, it was found that only 5 percent of the series or about two individuals could be considered normal by Kolb's criteria. This fact was of interest to Felix in his examination of group 2, which Kolb and Ossenfort called psychopathic diathesis or predisposition. Using the more strict definition, the proportion of the entire series falling into group 1 was 1 percent while 51 percent of the series fell in group 2.

Group 2, borderline individuals who, through some "ill-defined instability of personality" find difficulty in making a social adjustment, made up 38 percent of the five-category series.

Group 3, which was one to which subjects were assigned largely by exclusion, made up 13.5 percent of the total.

Group 4, the so-called criminal psychopaths contributed 13.5 percent, and the inebriates, the second largest group, made up the remaining 21.5 percent.

Pescor's excellent study reported in 1939 [14] using the revised classification of Kolb and Ossenfort utilized the clinical records of 1,036 patients admitted to the Lexington Hospital. Among the staff at the hospital and other investigators working with us, the six groups were given a prefix of "K." That is, group 1 became K–1, group 2 became K–2, etc. We use the K prefix here because of long usage and for nostalgic reasons. Only 3.8 percent of Pescor's series were considered as normal individuals accidentally addicted, and Pescor noted that even this low figure probably erred on the high side. From a statistical standpoint, Pescor noted that K–2 addicts, those with a psychopathic diathesis, could be called the "average addict" since 54.5 percent of the series fell in this group. To many of us who have had a reasonable amount of experience with addicts, his description of a typical K–2 addict sounds hauntingly familiar because, as we recall our years at the hospital, it seems as though nearly all patients were of this type.

According to Pescor, statistically, the characteristic which seems to distinguish this group is the tendency to rationalize their introduction to habitual use of drugs on the basis of curiosity and association with addicts. This statistically average K–2 would give a history of satisfactory childhood adjustment. His social adjustment prior to addiction would be adequate, although he would be tolerant toward all forms of vice. The chances were that he would not have a delinquency record prior to addiction, and his violations subsequently would be connected with obtaining drugs or the money to purchase them.

He would be of average intelligence and he would adjust well to institutional life. As time for release approached he would maintain vigorously that he had "learned his lesson" and that he was through with drugs for the rest of his life. The chances of his relapse were better than 50 percent.

Psychoneurotic patients, K–3, made up 6.3 percent of Pescor's series. This percentage was less than half that reported by Kolb (13.5 percent).

Patients diagnosed as psychopathic personality, K–4, comprised 13.4 percent of the series, although several in the group were psychotic and three claimed not to be addicted.

A total of 21.9 percent of the series were classified as inebriate personalities, K–5, and the newly added K–6, drug addiction associated with psychosis, contributed only one case to the series, although there is some question if the psychotics classed as psychopaths should not have been classed K–6.

As one stands here in the year 1975 and looks back at the beginning of this great research program as described in the words of the investigators, one can appreciate how frontiersmen in any field of endeavor must feel. Leaving familiar paths of endeavor which are accepted and "respectable" the adventurers launched forth into an uncharted wilderness, hardly knowing which way was north and sure only that they were alone and they were expected to think better of their rashness after a while and return to "civilization." Certainly many of us had moments when we felt somewhat that way at Lexington. In 1935–44 we took that first step all must take in serious research. We described as best we could the phenomena we were attempting to understand. This was as true of Himmelsbach and his ingenious abstinence-rating scale as it was of those of us working with the Kolb classification. The latter was an attempt to group addicts by psychological and social behavior in order to study the whole person in detail. Once categorized, attacks on the problem could be and were made by the biochemist, the pathologist, the pharmacologist, the psychologist, the neurophysiologist, and the psychiatrist. Admittedly, the K-classification can be criticized as being too subjective and impressionistic, but so can one criticize Kraeplin or Bleuler or Freud or Meyer. We who were working with the instrument were aware of our limitations.

Pescor, in discussing the concept of psychopathic diathesis said:

> "Individuals classified under 'psychopathic diathesis' are not innately antisocial. Their fundamental defect is an ill-defined emotional instability which finds expression in a search for new thrills, excitement, and pleasure. The emphasis on pleasure seeking suggest that 'hedonistic personality' would be more descriptive of such individuals than the term 'psychopathic diathesis.'
>
> "One of the chief objections to the classification 'psychopathic diathesis' is the ease with which it may be used as a diagnostic wastebasket for doubtful cases. Patients presenting features common to more than one category are almost invariably so classed, a subterfuge out of keeping with Kolb's intent. . . . Erroneous classification may be avoided by keeping in mind that 'psychopathic diathesis' is applicable only to individuals who have made an acceptable social adjustment prior to addiction, whose antisocial acts are confined to violation of drug laws, and who became addicted to drugs on a hedonistic basis.
>
> "Another failing . . . is the tendency to base a diagnosis of psychopathic personality almost purely on an antisocial record antedating addiction to drugs. In other words, the only psychopaths given complete recognition are the asocial or amoral types. It must be remembered that there are also sexual psychopaths and psychopaths with pathological emotionality, for example, schizoid, cyclothymiac, and paranoid personalities. These examples may also live up to the popular conception of a psychopath's 'ornery' tendencies."

Felix also expressed uneasiness especially with the diathesis category. He felt he knew what he was trying to describe, but he felt unsure that he was communicating satisfactorily. He used the following words to describe the K–2 group:

> "The concept of the psychopathic-diathesis group may not be as clear as that of the other two, but probably can best be described as a state in which, because of some ill-defined instability of personality, no better than a borderline adjustment is made. The individual is not fundamentally antisocial and, with some . . . assistance, can make an acceptable adjustment. The most striking characteristic of this group is the fact that, as a whole, they were adjusting marginally before they became ac-

quainted with narcotics. After their first few experiences with the drug, they felt an exhilaration and a sense of relief comparable to the solution of a difficult problem or the shaking off of a heavy responsibility. Many of them also felt an increase in efficiency which, in some cases at least, appears to have been an actual improvement. Having once found this new world of greater happiness and efficiency, they attempted to regain it and to live therein for all time.

"This phenomenon is not so prominent in the other two groups. The psychoneurotic takes his drugs to relieve himself of whatever type of symptom he may have. The psychopath . . . wishes to excel in deeds of daring, to be more clever than his fellows, or to stand out as an object of admiration. Under narcotics he feels that he has more nearly accomplished these ends. As Kolb [9] has put it, his use of drugs is 'comparable to the compensation of little men who endeavor to lift themselves to greatness.' In other cases, he uses this means to gain experience of pleasure over and beyond the requirements for comfortable living. He is a hedonist. What he desires to do he does for the pure pleasure to be derived from it. He . . . does not consider social or ethical standards a check upon his activity. . . . The patient with a psychopathic predisposition, however, takes his opium as a medicine which he believes—sometimes with good reason—helps him to make a more satisfactory total adjustment to life . . . and without which he feels inadequate to meet many of life's problems."

By 1944 it had become clear that conventional concepts of normality and abnormality in relation to personality characteristics did not appear to apply to addicts, at least not without considerable qualification. Before any of us had even entered the laboratory for the first time, Kolb [10] had said it for all of us in these words:

> "The psychopath, the inebriate, the psychoneurotic, and the temperamental individuals who fall easy victim to narcotics have this in common: they are struggling with a sense of inadequacy, imagined or real or with unconscious pathological strivings that narcotics temporarily remove; and the open makeup that so many of them show is not a normal expression of men at ease with the world, but a mechanism of inferiors who are striving to appear like normal men."

In the period prior to 1944 there was little investigative work being carried on to unearth the sociologic factors predisposing to addiction and relapse. The most common cause given by addicts themselves was bad companions with discouragement bringing up a poor second. A few hints were gleaned during this time, however. It appeared that the families where future addicts were reared had no strong and consistent father figure. The addict appeared not to develop internal controls due, in part at least, because he had no male model to use as a template.

The year 1944 is not the most desirable date with which to terminate this reflection on the early work at the center. The war was drawing to a close and research in all areas of science was looked upon favorably by the Congress. Dr. Kolb's successor as Chief of the Mental Hygiene Division had just been installed, and within a matter of a few weeks he was summoned to the Capitol to explain to the Appropriations Committee what progress was being made in the cure and rehabilitation of drug addicts. Pescor's followup study of treated narcotic addicts had appeared the year before [15]and to those of us who were familiar with our state of knowledge, we felt some satisfaction although certainly no smugness in his report that 13.5 percent of his series of 4,766 former patients released over the preceding 5 years were still abstinent. The committee felt less satisfied and the new chief spent an extremely uncomfortable afternoon in a very unfamiliar environment. The day seemed lost indeed until some angel who may in another incarnation have spent some time at Lexington and knew the problems, put into the shaken neophyte's head the idea of comparing our state of knowledge of the etiology and treatment of drug addiction to our state of knowledge of atomic weaponry in 1941 and suggested that more support might bring more results. The suggestion was received favorably, as you know, and a period of great and productive activity was ushered in. The years 1945–75 have been so productive that in retrospect, what we knew or hypothesized in 1935–44 seems meager indeed.

Those of us who are of the vintage 1935–44 salute you. The frontiers of knowledge in the area of substance abuse have taken a quantum leap forward thanks to your studies here. You epitomize so well the words of Joseph Bert Smiley:

"From contemplation one may become wise, but knowledge comes only from study."

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Dr. Lawrence C. Kolb, Jr., *Commissioner, Department of Mental Hygiene, State of New York*

Comments

Dr. Lawrence C. Kolb, Jr., M.D.

I came because of a long relationship with Bob Felix and other associates at the National Institute of Mental Health, and because of the wonderful memories of the days I spent at Lexington visiting as a medical student and first coming to know of the work in these laboratories. Later, I returned several times as a member of visiting scientific committees.

My own memories of the drug addiction research go back to the early twenties when my father was commencing to addict monkeys in the Hygienic Laboratories. He allowed me to come down on Sunday mornings and observe the behavior of the animals and observe him and others injecting those animals. I presume that this experience had a profound influence on my later career, although I did everything possible to avoid coming into direct relationship with Dad, by deviating into the field of medicine, then surgery, then neurology, and then into remote areas of psychiatry including psychoanalysis. Nevertheless, I ended up in psychiatry. The repetition and compulsion engendered through those many, many years under his guidance were effective.

I know that he influenced a number of persons here in varying ways as he did me. I told a story on Dale Cameron in his relationship to my father yesterday. It expresses something about my father's drive for excellence which was sometimes very, very painful to those experiencing his critical appraisals. Dale told me the story of once writing a paper and presenting it to my father for editing. When he returned the paper every line had a red mark, a pencil mark, or a question mark on it. Dale stated to me, "I put the paper in the drawer and didn't attempt to write again for 5 years." I had similar experiences and I think so did our speaker. These experiences clarified issues which later on served me in very good stead.

I can only express to you that it has been absolutely wonderful for me to be here with so many, many old friends and acquaintances. I have lived in admiration of the work of the Addiction Research Center for all these years, have many, many times quoted your work, and taught the information you have brought forward to the students who have come under my tutelage.

Dr. Clifton K. Himmelsbach, *Director, Addiction Research Center, 1935–44*

Summary of Chemical, Pharmacological, and Clinical Research, 1929–44

Clifton K. Himmelsbach, M.D., F.A.C.P.

While the scope of the title makes my task impossible within the time constraints, I do greatly appreciate your having invited me to try. But mainly, I'm happy just to be able to participate in this 40th anniversary of the opening of the first U.S. Narcotic Farm, to see old friends, and to recall the way it was and the things we did. I use the term "we" advisedly for that was the way our research was. Our research program was conceived as a team effort by Dr. Walter Treadway and that is how we functioned. While each of us "did his own thing," each did it in concert and often in collaboration with the others. Thus our researchers were multidisciplinary in both concept and execution. But, naturally, each of us is better known for the work for which he was primarily identified. For example:

—Our clinical physiologist, Edwin G. Williams, concentrated his attention on a tedious study of total energy and water exchange in a complete study of addiction, withdrawal, and recovery [27, 28]. He also initiated studies of cholinesterase activity and made important observations on marihuana.

Fred W. Oberst, our biochemist, first showed that morphine is excreted in "free" and "bound" forms [22]. His studies of the fate of other opiates and of meperidine were also noteworthy [23]. He collaborated with Williams on the long-range study.

Ralph R. Brown, our clinical psychologist, made a variety of interesting observations: For example, he found that addicts are anthropometrically and intellectually normal [4]. Utilizing the Rorschach test, he found that morphine tends to reduce neurotic responses and to facilitate fantasy and introversion [5]. Working with Williams on the long-range study, he demonstrated that morphine reduces reactions to stress.

Howard L. Andrews made his presence felt as a biophysicist first in the field of electroencephalography where he demonstrated that morphine addiction leads to a high percentage of alpha waves and to slow waves when large amounts are given [1]. Interestingly, the high alpha state often held for a year or more after withdrawal. Andrews' studies of pain led him to the interesting and important finding that morphine exercises relatively greater effect on one's reaction to pain than the perception of pain per se [2].

Robert H. Felix, as a result of intensive psychiatric studies, simplified the Kolb classification of addicts and emphasized the psychiatric basis for both addiction and relapse [10]. His behavior rating scale contributed significantly to our studies of codeine addiction [9].

Victor H. Vogel, an accomplished hypnotist, found that the hypersuggestibility which exists during maintained addiction disappears rapidly following withdrawal [26].

Michael Pescor, in a massive followup undertaking, confirmed Kolb's earlier observations that addiction generally starts in youth; that few persons attracted to it are psychologically normal; that antisocial behavior usually follows rather than precedes addiction; and that relapse is the rule—cure the exception [24, 25].

My own work involved studies of the morphine abstinence syndrome and its treatment, the addiction liability of narcotic drugs of known chemical structure, and studies of the nature of physical dependence.

I. Quantification of Morphine Abstinence Syndrome Intensity (M.A.S.I.)

During my fellowship in pharmacology with Sollmann and Eddy, I became familiar with much of the literature on drug addiction and was most impressed with the studies made in Philadelphia by Light and his associates [21]. Shortly after reporting for duty at the USP Annex in Ft. Leavenworth, Kans., in September 1933, I saw my first real, live—but very sick—addicts—a chain of 10 from New York City—and learned firsthand that Light was right. With experience I became impressed with the predictability of the clinical course of events following abrupt and complete withdrawal and this led me to devise a means for impersonally and objectively relating the intensity of the morphine abstinence syndrome to clinical judgment by grouping the signs of abstinence under the rubrics of "mild," "moderate," "marked," and "severe" and assigning scores of 1+, 2+, 3+, and 4+ to these respective groupings[19]; see figure 1.

This method worked out fairly well and although it was an improvement over narrative descriptions of the course of the illness, its ability to distinguish between the grades of severity was not as sharp as I had wished. So, adhering to Pythagoras' dictum that "numbers are the language of nature," I next tried to express this phenomenon numerically by assigning arbitrary values to the component withdrawal signs and, after several trials, arrived at the following system (figure 2), which gave the closest approximation to clinical judgment and was smoother than the 1+, 2+, 3+, and 4+ earlier method of assessing intensity [11].

Then, by plotting intensity scores against time, one could construct a visual representation of this dynamic clinical process (figure 3).

I must emphasize that the validity of the M.A.S.I. scoring system depends on tight control of research conditions and on the competence

THE ABSTINENCE SYNDROME

MILD, OR+
Yawning
Lacrimation
Rhinorrhea
Perspiration

MODERATE, OR++
Muscle tremor
Gooseflesh
Loss of appetite
Dilated pupils

MARKED, OR+++
Fever
Increase in respiratory rate
Restlessness
Insomnia

SEVERE, OR++++
Vomiting
Diarrhea
Weight loss

Figure 1

POINT SYSTEM FOR MEASURING ABSTINENCE SYNDROME INTENSITY BY THE DAY(D) OR HOUR(H)

Signs	(D) By day		(H) By Hour	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40% decrease in caloric intake)	3	3		
Restlessness	5	5	5	5
Emesis (each spell)	5		5	5
Fever (for each 0.1° C rise over mean addiction level)	1		1	10
Hyperpnea (for each resp./min. rise over mean addiction level)	1		1	10
Rise in a.m. systolic B.P. (for each 2mm Hg over mean addiction level)	1	15	1	10
Weight loss (a.m.) (for each lb. from last day of addiction)	1			

Total abstinence syndrome intensity per day or per hour is the sum of the points scored in the (D) or (H) columns respectively, with due attention to the limits.

FIGURE 2. *Reproduced from Himmelsbach and Andrews* [18].

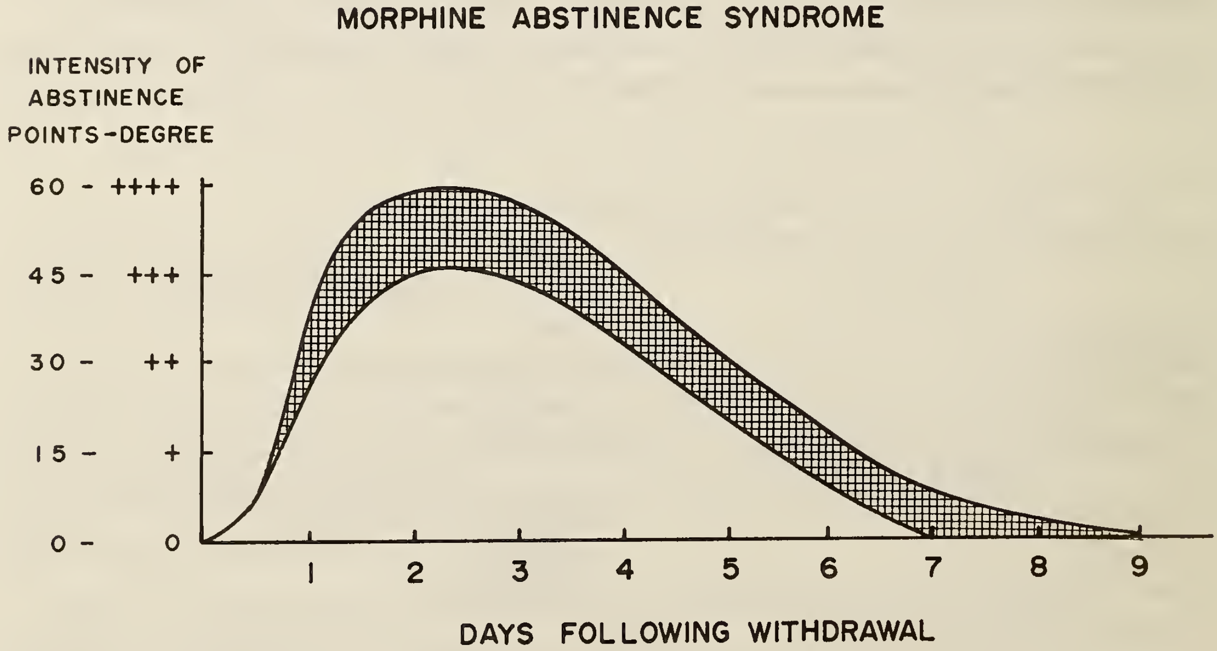

FIGURE 3.

and diligence of the observers. In both of these requirements I was particularly fortunate since the research conditions at Ft. Leavenworth and at Lexington were very good and the assistants were excellent. Thus, much of the success of our work depended on and was assured by the diligence of the following guard-attendants: C.E. Allday, Robert Blake, Harold Bowhay, J.C. Buchanan, Henry Elam, Clinton Gray, Charles Keebaugh, Vincent McFadden, Clyde R. Logan, W.C. McKay, Howard Moninger, Frank Pescor, and Ward Workman. They were ably assisted by Othilia Mertes, R.N., and Eugene B. Douglass.

Later, Howard Andrews collaborated in refining the use of the scoring system by relating the total M.A.S.I. to the addiction stabilizing dosage level, thereby making it possible to predict expectancy and measure effects of treatment, if any, with precision—a distinct advantage over "eyeballing" the curves [3]; see figure 4.

Andrews also helped adapt the system to enable it to serve as a means for quick estimates of addiction liability by administering a single dose of a test drug at the 30th hour of abstinence and measuring the effect, if any, on the predictable course of M.A.S.I. events [18]; see figure 5.

In summary, then, the M.A.S.I. scoring system constituted the basic research tool we used for the detection of addiction liability and studies of treatment. It constituted a reliable method for assessing dependence, served us well, and seems to have stood the test of time.

II. Substitution Studies

The Drug Addiction Committee of the National Research Council elected to try to produce a nonaddictive substitute for morphine as a means of eliminating the need for morphine and thereby solving the problem of drug addiction [7].

They chose to approach this scientifically by producing many stipulated chemical variations of the morphine molecule and then relating pharmacologic actions to chemical structure. Hopefully this would point the way to effectuating a dissociation of the analgesic from the dependence-producing actions of the opium alkaloids. Implementation of this program required two extensive laboratories: one in alkaloidal chemistry headed by Dr. Lyndon F. Small at the University of Virginia, and one in pharmacology headed by Dr. Nathan B. Eddy at the University of Michigan. As a hedge against possible failure of this approach, Dr. Erich Mosettig worked with Dr. Small to produce synthetic agents which might be found to have analgesic effects but no addiction potentiality. Then, the numerous agents of known chemical structure provided by Small and Mosettig were sent to Eddy and his associates for studies of their effects on the respiratory tract, the cardiovascular system, the

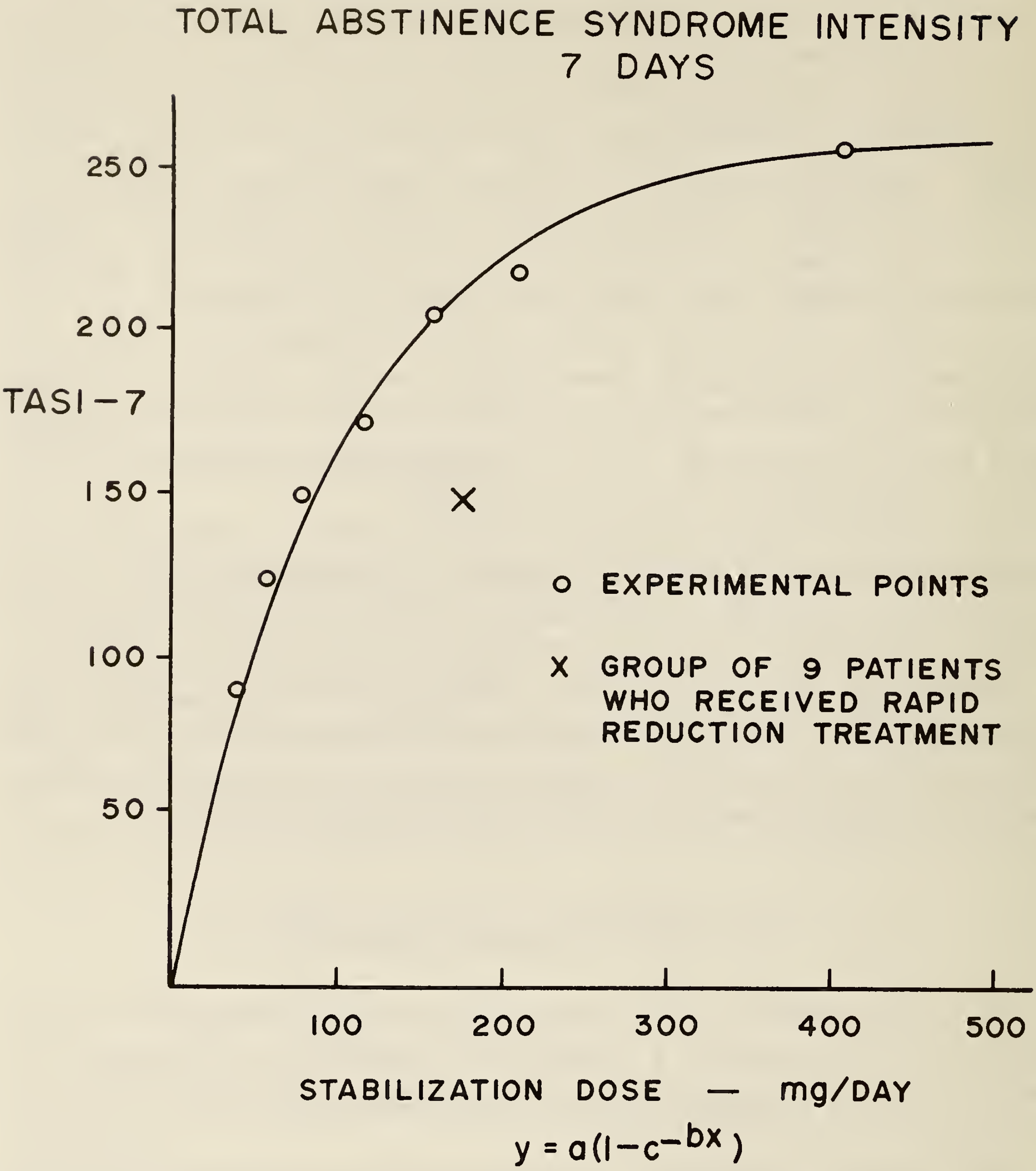

FIGURE 4. *Reproduced from Andrews and Himmelsbach* [3].

gastrointestinal tract, etc. and as to their ability to effect a reduction in sensitivity to pain and to produce addiction in animal models. Dr. Small's work started in 1929 and Dr. Eddy's in 1930. By 1932 clinical trials seemed warranted on the basis of the pharmacological results, and I was recruited by Dr. Treadway to accept a fellowship in pharmacology and then be responsible for this end of the work.

Those of you who knew them can well imagine the pressure I was under from Walter Treadway and Nathan Eddy to get to work shortly after arriving at the USP Annex, Ft. Leavenworth, Kans. It occurred to me that as a starter it would be interesting to check in man the Downs and Eddy [6] observation that in addicted dogs cross-tolerance existed

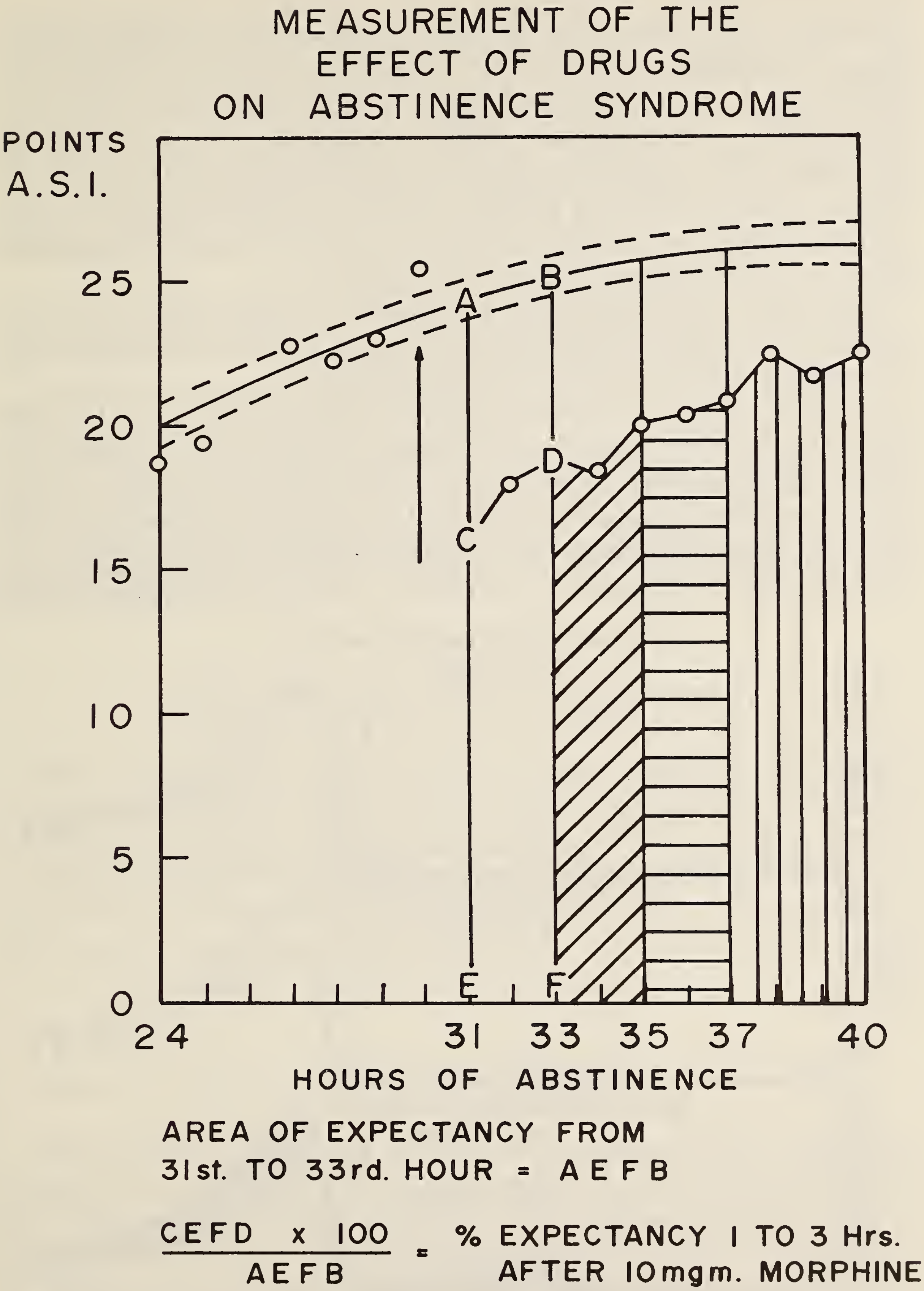

FIGURE 5. *Solid line is group 1 expectancy curve; dashed lines are + and − σ (dis.). Open circles are group mean data points before and after 10 mg morphine. Four out of seven predose points are within σ (dis.). Reproduced from Himmelsbach and Andrews* [18].

between morphine derivatives. So, after establishing the presence of dependence by withholding morphine from newly admitted prisoner addicts, I stabilized them on minimally effective doses of morphine for about 1 week, then substituted one of Small's derivatives in amounts which Eddy's pharmacologic studies suggested as being biologically equivalent. When I guessed right about the dose relationships the switch was scarcely noticed by the patients, and when the substituted drug was withheld about 1 week later, an abstinence syndrome indistinguishable from that of morphine appeared; see figure 6.

With some derivatives—such as codeine—the transition was not so smooth, but nonetheless dependence of a sort was sustained by all of the morphine derivatives tested by this technique.

All of this led me to the view that an agent which would sustain physical dependence could also produce it. When it was shown that desomorphine sustained dependence quite adequately despite having failed to produce addiction in monkeys, it was arranged that I go to the Pondville (Massachusetts) Cancer Hospital and compare morphine and desomorphine when used for the relief of pain in nontolerant terminal

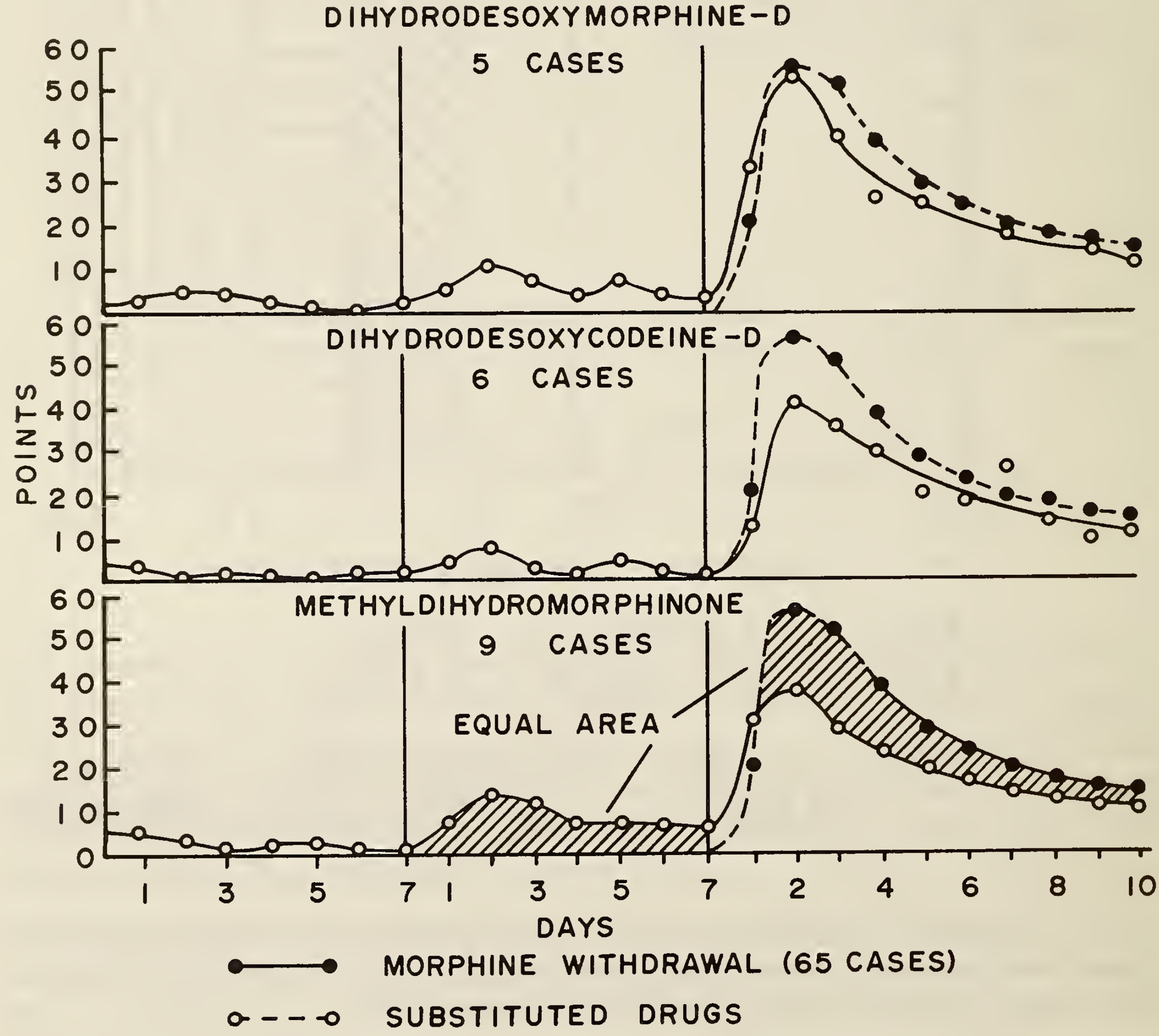

FIGURE 6. *Reproduced in part from Himmelsbach* [11].

cancer patients. Given under these circumstances, dependence to desomorphine did occur. Desomorphine relieved pain splendidly, but its administration at intervals required for analgesia resulted in tolerance and dependence much more readily than did therapeutically equivalent doses of morphine in control patients [8]. While this critical test seemed to validate the hypothesis of the substitution method, the issue was again raised when Demerol was shown to possess addictional liability [14, 15]. Here again, clinical experience later confirmed the substitution result.

Unfortunately, none of the many morphine derivatives studied turned out to be the "bee without a sting." Nor did there seem to be a clear lead that the chemical changes studied effectively dissociate analgesic and dependence-producing actions [12]. We were looking for a derivative in which both the duration and the intensity of physical dependence action would be reduced and long and strong analgesic action would be retained. Unfortunately, however, potency seemed to be associated with brevity, hence to be conducive to more frequent administration and thereby facilitative of the induction of dependence and tolerance.

III. Treatment of Withdrawal

Even 40 years ago it was difficult to understand the fairly prevalent view that separation of the dependent addict from his drug was difficult or that such separation effected "cure." But foolish as it seems, we were expected to check out various forms of so-called therapy. It came as no surprise that most treatments were as bad or worse than nothing and that the best agent available at that time to ease the intensity of withdrawal was morphine itself [18, 20]; see figure 7.

IV. Recovery

Shortly after the opening of the Lexington Hospital Dr. Kolb held a meeting for the purpose of estimating the optimum treatment period for volunteers and probationers since they could be discharged when, in the opinion of the Medical Officer in Charge, they had recovered sufficiently to function in society without relapse. We guessed that 6 to 9 months of treatment at Lexington would be adequate. Since objective data on the recovery process were needed, a longitudinal study of a battery of physiologic processes disturbed by addiction and withdrawal was undertaken through the 9th month of abstinence. The results suggested that 4 to 6 months was a good guess for recovery of most of these physiological parameters [13]. But if reduced resting blood flow to

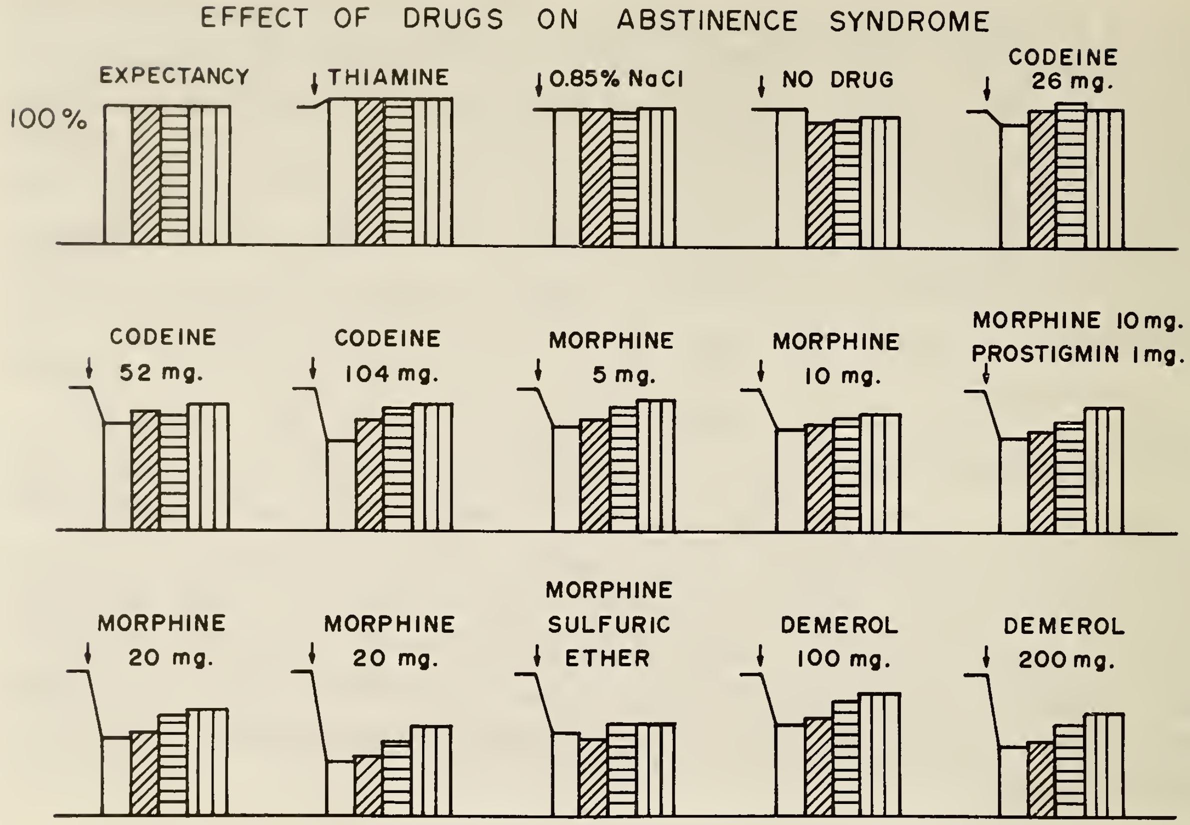

FIGURE 7. *Reproduced in part from Himmelsbach and Andrews* [18].

the hand is indicative of increased nervous tension—and there is reason to believe that is so—then 6 months is insufficient to regain autonomic stability [17]; see figure 8. Also, Andrews' observation that the high alpha state does not usually return to normal within 1 year must have significance.

(a) BLOOD FLOW TO HAND

	No.	Mean	σ(dis.)	σ(av.)
Normal (Abramson and Fierst) [14]	61	9.3	2.1	0.18
Normal (Himmelsbach)	22	9.5	3.2	0.5
Incarcerated marihuana users	19	9.8	3.6	0.58
Postaddicts (opiate)	51	8.1	3.5	0.25
Stabilized opiate addicts	17	6.3	2.4	0.47

(b) CRITICAL RATIOS OF DIFFERENCES

	(A)	(B)	(C)
(A) Normal (Himmelsbach)			
(B) Incarcerated marihuana users	0.39		
(C) Postaddicts (opiate)	2.5	2.7	
(D) Stabilized opiate addicts	4.6	4.7	3.4

FIGURE 8. *Reproduced from Himmelsbach* [17].

V. Physical Dependence

These plethysmographic studies, together with withdrawal signs and morphine effects, suggest that physical dependence may have its roots in the autonomic nervous system. It seemed possible to us that dependence could be an adaptive phenomenon resulting from repetitive corrections of opiate-induced disturbances to homeostasis. One could surmise that with such repetition the capacity to respond to, or to counteract, morphine effects becomes so strengthened that at some critical point morphine is necessary to subdue the responses and thereby maintain a semblance of homeostasis [16].

VI. In Summary

These were the small beginnings. We enjoyed trying, but found the nut much too tough for us to crack. However, the words of Newton bring some solace: "'Tis much better to do a little of certainty, and leave the rest for others who come after you, than to explain all things." We certainly left our successors plenty to explain! However, as we have learned here, and as we have seen in our tour of the Addiction Research Center, our successors have responded so magnificently to the challenge that we of the antecedent generation are convinced that the situation is in very good hands.

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Dr. Edwin G. Williams, *Director,*
Addiction Research Center, 1944–45

Discussion—Dr. Himmelsbach's Paper

Edwin G. Williams, M.D.

I have been asked to discuss Dr. Himmelsbach's paper. With your permission I shall decline to do so. The paper is an entity within itself and any attempt on my part could serve only to detract from it.

With your indulgence, I should like to reminisce with the older ones of you and for the present generation concerning some of our earlier struggles, experiences, and associations, and perhaps reveal to you some of my naiveté. First, let me express my deep feeling of gratitude and appreciation for the privilege of being here.

Research work at this station was started by Douglass, Himmelsbach, Ralph Brown, and me, under the inspiration and masterful "non-guidance" of Dr. Kolb. Soon we were joined by Felix, Vogel, Pescor, Wikler, Andrews, Oberst, and others. Dr. Himmelsbach described our interdisciplinary-individualistic modus operandi. Perhaps the largest and most complex single study was "A cycle of morphine addiction." A few days ago I read the published outline for this study and fairly shuddered at its magnitude and at the brashness of these neophytes. On reflection. I think I know why my name is the only one appearing on the article! Let me read you one sentence: "An intensive study of physiochemical, psychological, and psychiatric changes resulting from single therapeutic doses of morphine, from repeated doses of morphine, during stabilized addiction, and during the post-addiction state will be undertaken . . ." And that was not written in support of a budget request!

One incident we did *not* publish: Those of you who have worked with metabolism chambers know how difficult it is to get and keep them gas tight—ours was no exception. After several weeks of testing by Dr. Oberst, and re-soldering by the shop group (and mind you this was a man-sized, live-in chamber), the shop superintendent (who was also an artist) came by and was horror struck at its stark ugliness. Without discussing it with us, he had *154* additional holes drilled through the chamber wall to hang some decorative trim! The fact that Oberst is alive today is a testimonial to the rugged stability of his ancestors.

I had read and had reported to our Journal Club a short article in *Science* about Berger rhythm. Dr. Felix had "sold" the idea of electroencephalography as a drug addiction research tool. I will quote again from my statement of our plan of attack (this was before Dr. Andrews had been recruited): "By means of this apparatus a relatively simple and easily interpretable method of studying conditioned reflexes (and other phenomena) is at hand." I recommend that none of you ever read anything that you wrote—or at least that I wrote—5 or more years ago!

Although our major interests were still focused on opiate drug addiction, marihuana was becoming sufficiently important from a social (including legal) standpoint that we decided to take a "look-see"—by now it seems to have been a "peep-see." It was shown that the synthetic substance called pyrahexyl compound was sufficiently similar in its action on man to serve as a useful research tool, the prime advantage being reproducibility of dose.

Permeating this entire symposium is the ever present—one is tempted to say the everlasting—influence of Dr. Kolb whose work took drug addiction out of the occult and changed dope fiends into drug addicts.

Since I left here in 1945, a marvelous metamorphosis has taken place. What were new research tools 40 and 30 years ago have been superseded by advancements and refinements that are staggering. Through it all, one sees the administrative genius of a Treadway perpetuated by a Felix, the milk of human kindness of a Kolb and an Isbell, the eagerness of a Himmelsbach held in restraint by an Andrews and continued by a Wikler, and one perceives the steadying hand of a Martin.

The Williamses are glad to have been associated.

Thank you.

DR. HARRIS ISBELL, *Director, Addiction Research Center, 1945–63*

Clinical Research, 1944–63

Harris Isbell, M.D.

When I returned to Narco in 1944, Research, as it was called, was a small unit with only 15 employees. Research lived off the bounty of the hospital and had only a minimal budget for supplies and equipment, Dr. Wikler had just returned from training at Chicago, Yale, and Johns Hopkins and was beginning his classic work on the neurophysiology and psychology of opiate dependence. Facilities for basic animal research were makeshift and inadequate. On the positive side, there was a fine clinical research unit in existence with a group of highly trained aides and a technique for evaluating the dependence liability of opiates. This was the legacy that Dr. Himmelsbach left us. We also had functioning small sections on clinical biochemistry and clinical psychology. The important biophysics section was without a head. The war had taken away important personnel—Ralph Brown in psychology, Fred Oberst in biochemistry, and Howard Andrews in biophysics.

Because of the war Drs. Small and Eddy at the National Institutes of Health had discontinued synthesis and pharmacological studies of new congeners of morphine so that the program of seeking a nonaddicting analgesic for which the unit had been founded was in abeyance. The first synthetic, meperidine, had been studied by Himmelsbach [18, 19] and found to have dependence liability of the morphine type.

Dr. Himmelsbach [20] had studied chronic intoxication with amphetamine and with mixtures of morphine and amphetamine and had, as an unexpected result, demonstrated experimentally the amphetamine psychosis. Interest in marihuana had increased slightly. Himmelsbach (cf., Williams et al. [42]) had studied the synthetic pyrahexyl and had shown that it had marihuanalike effects and that no clearcut physical dependence occurred in chronic administration. Dr. Williams and his coworkers [42] were in the midst of an experiment on chronic smoking of marihuana. In this experiment definite behavioral changes occurred initially followed by apathy as the experiment went along. No physical dependence on marihuana was demonstrated.

Programmatic and Administrative Changes

In 1945 I succeeded Dr. Williams as Director of Research. Because of limited resources, there was initially little that could be done to improve and expand the program. Research was still dependent on the hospital for funds, and it was, of course, difficult for the hospital whose primary mission was service to patients to justify large increases in its budget for research. All this changed dramatically with the creation of the National Institute of Mental Health in 1948. Research became a unit of that Institute and was renamed the NIMH Addiction Research Center. For some time we were the only unit of NIMH actively engaged in experimental research. The fact that we were now in an organization whose primary mission was research and not service meant that it was easier to justify budget increases to Congress than it had been. In addition, the administrative people in the National Institute of Mental Health were sympathetic to our program. Drs. Felix, Cameron, and Lowry at NIMH watched over our interests and supported and protected us. The scientific directors—Drs. Kety, Livingston, and Eberhart—all gave us enthusiastic help. So our budget and program grew slowly but surely. There is no doubt that becoming a part of the National Institute of Mental Health was the greatest thing that happened to the Addiction Research Center.

However, I also wish to pay tribute to the contributions of the hospital to the research program during this period. The Medical Officers in

Charge—Drs. Vogel, Chapman, Diamond, Lowry, and Rasor—were all sympathetic to research. The hospital furnished us room, board, and laundry and allowed us to borrow some of their patients, a situation that frequently caused administrative problems for the MOC's. I believe that if it were possible to total the relative financial contributions of the hospital and the NIMH to the research program, the contribution of the hospital might be the greater.

Although I was, in my own work, concerned chiefly with clinical research, I felt that, in the long run, the answers to drug dependence had to come from basic research and that I would do all that I could to strengthen and increase this part of our research program. I already had a great leader for basic research in Dr. Wikler. Our first requirement was to give him more help and facilities. So as opportunity afforded we brought in Karl Frank in biophysics. He was later succeeded by Harold Flanary. Frank Fraser became my able assistant and colleague in clinical research. Harris Hill arrived to take charge of the psychology section ably abetted by two young men, Chris Kornetsky and Dick Belleville. Dr. Carl Essig arrived and initiated animal work on sedative, hypnotic, and alcohol [6, 7, 8] dependence. Dr. Martin came to strengthen the neurophysiology-neuropharmacology section.

One of our great needs was for adequate facilities for animal experimentation. This was partially solved in 1951 when a temporary, frame, animal laboratory building was erected. This alleviated the problem for a time but we soon outgrew the new facility and began maneuvering for a larger permanent structure which was finally completed in 1964. As you have seen in your tour, Dr. Martin has received even greater support from NIMH and NIDA.

I don't think that this recapitulation would be complete without mentioning the role of supporting personnel. Our aides, our technicians, our animal men and our secretaries were absolutely essential ingredients in our work throughout this time. Without them we could have accomplished little.

Changes in our clinical pharmacological program during this period were partly deliberate and partly forced by the exigencies of the time. The deliberate change was enlarging the area of study to drugs other than opiates or opioids including the barbiturates and other hypnotics, alcohol, the hallucinogens, and compounds found in marihuana. The part that was forced on us was the rapid development of many chemical types of synthetic opioids and narcotic antagonists that had to be evaluated for dependence liability. Although we were able to continue some work on the clinical physiology of opiate dependence, such experimentation definitely suffered because of the pressures for drug testing.

Clinical Physiology

The first experiment of my own in the clinical physiology of drug dependence was concerned with body water. Drs. Oberst and Williams had found that dependence on morphine was associated with variable changes in extracellular water, as measured by the thiocyanate method, and with an increase in the water content of whole blood but without changes in the percentage of water in blood serum or cells. Dr. Williams asked me to repeat this work. I found that changes in the extracellular, or thiocyanate, space were too erratic and too variable to interpret [23]. The total red cell mass declined slightly but significantly. The increased water in whole blood was due to a greater proportion of serum relative to cells. Serum volume was unchanged in stabilized dependence but red cell mass decreased. In short, the increased amount of water in blood was due to a mild anemia during maintained addiction. Because of interest in body water, we investigated the antidiuretic action of morphine in man. It had already been shown that, in animals, morphine caused release of antidiuretic hormone from the anterior pituitary. Later it was found that part of the antidiuretic effect of morphine in animals was due to changes in blood flow in the kidney. In any event, in nontolerant former addicts morphine had antidiuretic effects ranging from mild, with doses of 10–15 mg, to marked, with doses of 30 mg, s.c. During maintained administration of 30 mg of morphine four times daily, the antidiuretic effect was marked early in the experiment during the daytime, but patients diuresed at night, losing all the water they had retained during the day. So no net accumulation of water occurred. This phenomenon occurred in the very first day of the experiment so it is difficult to attribute it to tolerance. Rather, it is probably due to a diurnal variation in the secretion of antidiuretic hormones or in blood flow.

For 2 or 3 years we were concerned with attempts to evaluate the analgesic potency of drugs by studying the threshold for perception of pain. After a rather great effort, we were forced to conclude that opiate analgesics did not alter significantly the threshold for pain regardless of whether that threshold was measured by the Hardy-Wolff-Goodel method—a hot light of variable intensity focused on a blackened spot on the forehead—or by the voltage required to elicit pain by electrical stimulation of a tooth. We found that it was necessary in this work to have apparatus arranged in such a fashion that neither the patient nor the operator could memorize unconsciously the distance that a control had to be turned initially to elicit pain. Our results in this area were similar to those of Dr. Henry Beecher.

Dr. Fraser became interested in the effects of morphine on adrenal cortical function and, in collaboration with Dr. Anne Eisenman, carried out extensive studies of the effect of cycles of morphine addiction on the excretion of 17-ketogenic and 17-hydroxy-steroids [3, 5]. Urinary output of these substances during stable maintained addiction to morphine was depressed significantly indicating some degree of adrenal cortical depression. The adrenal cortex, however, responded to ACTH in nearly normal fashion indicating that the depression might be due to partial suppression of ACTH by the anterior pituitary [4]. It was not caused by an increase in the rate of metabolism of adrenal corticoids in the liver since the half-life of hydrocortisone given intravenously was unaltered. During acute abstinence from morphine, urinary excretion of adrenal corticoids increased markedly.

Opiates and Opioids

During the war the program of the NIH and National Research Council's Committee on Drug Addiction of developing a "nonaddicting" analgesic had been discontinued, and the chemical and pharmacological sections at NIH had turned their attention to antimalarials to further the war effort. No new opiates had been submitted for evaluation. In 1946 the situation changed dramatically with the advent of methadone, or amidone, as it was then called. This synthetic, chemically unrelated to morphine, had been developed in Germany and used as a replacement for morphine by the German Army during the war. It was brought to this country for evaluation by our intelligence teams. Methadone had a spectrum of morphinelike effects in animals, including analgesia and respiratory depression. Because the chemical structure of methadone was different from that of morphine, there was some hope, despite the example of meperidine, that methadone might not have dependence liability, so it was submitted to the Addiction Research Center for evaluation. Studies in nontolerant former addicts showed that methadone produced a morphinelike spectrum of subjective and objective effects [29, 35, 37]. When given intravenously, methadone induced intense euphoria which was rated as being equal to or greater than euphoria following morphine or heroin. When substituted for morphine in subjects stabilized on 240 mg of morphine daily, abstinence was completely suppressed in doses only one-third those of morphine. When methadone was abruptly withdrawn, a definite abstinence syndrome appeared more slowly than abstinence from morphine. Abstinence from methadone was objectively, in terms of Himmelsbach's point score method, much less severe than abstinence from morphine. Subjectively, patients complained bitterly and over a long period. Similar abstinence was seen after direct addiction to methadone. It was, therefore, evident that methadone had dependence liability of the morphine type and should be controlled. Since methadone was the second synthetic with a chemical structure different from morphine, it was evident that a large number of synthetics differing chemically from morphine might be developed and to bring these under control by passing individual laws for individual drugs was too cumbersome a procedure. The narcotic law was therefore altered to provide that "any drug that had 'addiction-forming' or 'addiction-sustaining' properties similar to morphine or cocaine" could be declared an opiate.

Experience with methadone and the change in the law marked the beginning of a subtle shift in our thinking that was reinforced as time went on. The hope of developing a nonaddicting analgesic began to fade and, more and more, we began to think of our work as a preventive public health measure designed to prevent the introduction of drugs possessing dependence liability of the morphine type into general use without proper control.

It was evident that the dependence-supporting action of methadone lasted much longer than that of morphine and that methadone was relatively much more effective orally than morphine. These properties of methadone were exploited in the development of the method of withdrawing opiates from physically dependent subjects by substitution of methadone [34] for whatever opiates the patients had been taking followed by reduction of the methadone. Originally methadone was given parenterally; later it was given orally. This withdrawal method remains the most widely used means of withdrawing opiates today. In addition, the oral efficacy and long length of action of methadone remain the pharmacological basis for use of methadone in maintenance management of opiate dependents.

The Synthetic Flood

Following the development of methadone, many new chemical types of analgesics were rapidly developed. By 1963 there were ten or more different chemical families of analgesics, some closely related chemically to morphine and others not. Included were the hexamethyleneimines [10], the dithenyl-butenes, the morphinans [11], the benzomorphans [12] and others. In addition, many new congeners, including congeners of morphine, were developed in each chemical class. Our capacity to test these drugs was strained to the limit and only the development of screening methods in monkeys at the University of Michigan prevented us from being completely overwhelmed. There is no need to recapitulate the findings with all these drugs. In general, if a new drug, or type of drug, produced a morphinelike spectrum of effects in animals, including analgesia, that drug had dependence liability of the opiate type in man and the degree of dependence liability paralleled, in a rough way, its analgesic potency.

Assessment of the Subjective Response

When we began with methadone, we were impressed by its ability to induce subjective effects that addicts recognized as being morphinelike. Similar phenomena occurred with other synthetics, especially the more potent ones. Originally, assessment of the subjective response was informal and haphazard and was dependent on casual untimed interviews by staff and by aides. The system obviously needed improvement. The first step was the development of a simple questionnaire administered at definite times before and after single doses of new drugs plus simple behavioral observations [15]. The second step was, under the influence of Dr. Henry Beecher [1], to install the "double-blind" procedure. These simple measures served us well but we were not satisfied. We felt that we needed a more scientifically calibrated instrument so the aid of our psychologists, Harris Hill and Dick Belleville, was enlisted. Later, Dr. Haertzen took over the project. In my innocence, I thought that this was a simple matter that the psychologists could complete in a few weeks in their spare time. Instead it turned into a mammoth project [21, 22] which is still in progress. We will hear more about it later today.

Weak Drugs

As time went on the research units of the pharmaceutical companies began to stress the development of weak, synthetic analgesics, antitussives and antidiarrheal agents that might compete with codeine. This was a natural development since the market for codeine is huge, while that for morphine is small. The evaluation of the dependence liability of these agents is much more difficult than that of strong drugs because the effects may not be marked and assessment of dependence liability is hampered by toxicity because of the large doses that have to be used. Dr. Fraser will be telling us more about these problems.

The Antagonists

Even before we began work with methadone, we had obtained a supply of the first potent antagonist, nalorphine. We were interested in nalorphine because of conflicting reports of its analgesic potency in animals. Methadone and the subsequent synthetic flood caused us to put nalorphine on the shelf for a while but eventually we got back to it. We found that single doses of nalorphine produced a spectrum of subjective effects that was partially morphinelike and partially not. The outstanding difference from morphine was the production of bizarre mental symptoms in some patients [26]. Nalorphine did not support dependence on morphine [30]. Rather nalorphine precipitated abstinence in opiate addicts [41]. One direct addiction experiment [26] was done with essentially negative results but, because of lack of material, we could not give the drug at sufficiently short intervals for sufficient time so a satisfactory direct addiction experiment was not done until after I had retired.

We felt that nalorphine was interesting because it did produce some morphinelike effects and, therefore, might conceivably have analgesic effects in man. It also seemed possible that mixtures of morphine and nalorphine might produce less physical dependence liability than morphine alone. Tests of the mixtures in former addicts [14] revealed that, as time went on, abstinence was precipitated with each dose so that the use of such mixtures would be impractical in the treatment of chronic pain. Lasagna and Beecher [39] at the Massachusetts General Hospital, however, showed that nalorphine had analgesic potency equivalent to morphine for relief of postoperative pain. Frequent occurrence of hallucinations, however, precluded routine use of nalorphine.

These observations stimulated efforts to find an antagonist with the analgesic effects of nalorphine but without the bizarre mental effects of nalorphine. Many antagonists were synthesized and tried. It soon became evident that many antagonists had some morphinelike or agonistic effects. All of these, however, have had to some degree the disadvantages of nalorphine. The only agonist-antagonist that has reached the market is pentazocine but pentazocine does produce a type of physical dependence milder and qualitatively different from that of morphine [13]. Other antagonists, such as naloxone, have no morphinelike effects and are "pure" antagonists.

Interest in the antagonists is still high and we will be hearing more about them from Drs. Martin and Jasinski.

The antagonists have two proven uses: (1) As antidotes in the treatment of overdoses with opiates and opioids [24], and (2) in diagnosing physical dependence of the opiate type in man [25]. A third possible use is the prevention of relapse following withdrawal of opiates from morphine dependents. This last possible use will be discussed later by Dr. Jasinski or Dr. Martin.

Dependence on Drugs Other Than Opiates and Opioids

Throughout the period from 1945–63 chronic intoxication with drugs other than opiates was increasing in incidence, importance, and in the degree of public concern created. Included were barbiturates, alcohol, the hallucinogens, the central stimulants, and marihuana. We, therefore, had to engage in studies of the clinical pharmacology of these compounds.

Barbiturates

The first of the nonopiate types of drug dependence to assume importance was chronic barbiturate intoxication. During the war, the shortage of opiates in the illicit market caused by close control of shipping and other modes of transportation was associated with an increase in the number of the opiate dependents who were also taking barbiturates in large amounts. Since barbiturates were not supposed to create physical dependence, barbiturates were abruptly withdrawn and some patients had convulsions and/or a delirium. Similar phenomena had been reported in the literature. So it was important to find out whether barbiturates actually caused physical dependence and, with a great deal of trepidation, we undertook experimentation in man. The results are, I think, familiar to you [28]. In sufficient doses in nontolerant patients, barbiturates cause drunkenness, nystagmus, incoordination, etc. During chronic intoxication, tolerance to these effects developed rapidly only to reappear when the dose was increased. In contrast to opiate intoxication in which tolerance seems nearly limitless, tolerance to barbiturates had an individual ceiling in each individual patient which could not be exceeded without intoxication recurring. On abrupt withdrawal of barbiturates, restlessness, weakness, postural hypotension, EEG abnormalities, convulsions, and delirium appeared. The clinical picture resembled that of alcoholic delirium tremens. Recovery was complete. These serious symptoms could be prevented by gradual withdrawal of barbiturates. Exploration of the minimal dosage necessary to cause definite withdrawal symptoms indicated that minimal dosage was about 0.3–0.4 grams of a potent barbiturate daily [16].

Therefore a new type of physical dependence had been identified. On the basis of clinical reports and of animal experiments [6], the same syndrome is associated with chronic intoxication with a large number of chemical types of sedative and hypnotic drugs including chloral hydrate, paraldehyde, glutethimide, meprobamate, chlordiazepoxide, and others.

Alcohol

The clinical resemblance of barbiturate intoxication to intoxication with alcohol and of barbiturate withdrawal to alcoholic delirium tremens suggested that alcoholic "rum fits" and delirium tremens might also be manifestations of abstinence. Clinical opinion on this point was divided and in the United States the prevailing opinion was that abstinence from alcohol was not responsible for "rum fits" and delirium tremens. The question was important because of the high mortality rate associated with delirium tremens so we put the question to the direct test by intoxicating patients chronically with large amounts of alcohol [31]. These patients, of course, initially were drunk but soon developed a type of biochemical tolerance with low blood alcohol concentrations after doses that originally caused high blood levels. When the dose of alcohol was increased, blood alcohol levels rose again and patients were again drunk, and biochemical tolerance did not increase further but the patients soon developed another type of tolerance manifested by greatly decreased signs of intoxication even with high blood alcohol levels. When alcohol was abruptly withdrawn, patients developed weakness, tremors, perspiration, fever, EEG abnormalities, and some had convulsions, and/or a delirium. These were clearly manifestations of abstinence.

The clinical resemblance of alcoholic intoxication and abstinence to barbiturate intoxication and abstinence led us to try cross-tolerance and cross-dependence between alcohol and barbiturates [17]. Partial suppression of abstinence from barbiturates with alcohol indicated that a biological relationship existed. The term *barbiturate-alcohol type of drug dependence,* was then applied to chronic intoxication with drugs associated with convulsion and delirium on withdrawal [2].

Dr. Carl Essig undertook to study these intoxications in animals. He developed methods for developing physical dependence on barbiturates in cats [7] and other animals, and on alcohol in dogs [9], and was able to prove that our assumption that barbiturates in sufficient dose would suppress abstinence from alcohol was correct [8].

After a great deal of early resistance, the fact that "rum fits" and delirium tremens are manifestations of abstinence from alcohol is now universally accepted, and the treatment that we advocated based on cross-tolerance and cross-dependence of substituting hypnotic or sedative drugs for alcohol in doses initially sufficient to cause intoxication followed by gradual withdrawal of the substitute drug is now nearly standard.

The demonstration of a new type of physical dependence also began to affect our thinking. We could no longer think of "addiction" as being limited to opioids. Subsequent events required that this view be enlarged to include drugs that did not cause physical dependence, leading eventually to the formulation of the concept of drug dependence by the expert panel of the World Health Organization [2].

The Hallucinogens

Peyote, which contains mescaline, was included among the drugs justifying admission to the hospital. No such patients ever appeared. A few experiments with mescaline, dealing largely with excretion and metabolic fate, had been done in collaboration with Dr. Seevers and coworkers at the University of Michigan. In 1954, at Dr. Seevers' suggestion, we obtained a supply of the diethylamide of lysergic acid (LSD) and began to study it. We found [27] that LSD induced the same symptoms in former morphine addicts that were reported in Swiss physicians, medical students, and neurotic patients. These symptoms included euphoria, anxiety, feelings of unreality, depersonalization, and vivid optical hallucinations. The signs included pupillary dilation, increased blood pressure, and enhanced deep tendon reflexes. We developed questionnaires for measuring subjective effects and were able to obtain quantitative dose response curves on both subjective and objective measures. At that time, LSD was spoken of as inducing a "model psychosis" similar to schizophrenia. Dr. Wikler was not impressed by the resemblance to schizophrenia since patients under LSD did not develop bizarre explanations for their experiences. Dr. Wikler suggested that our patients might begin to develop schizophreniclike thinking if they took LSD daily. So the experiment was done. It was a failure in terms of the original object because the patients developed a high grade of tolerance very rapidly and, after a few days, were getting no effects from LSD [27]. No abstinence was observed on abrupt withdrawal.

Being disciples of Himmelsbach, we conceived the notion that we might be able to show relationships between LSD and other hallucinogens by the technique of cross-tolerance. We then demonstrated tolerance to psilocybin [38] and psilocin and a high degree of cross-tolerance between these two drugs and LSD. Tolerance also developed to mescaline with accompanying cross-tolerance to LSD [43]. Tolerance to dextroamphetamine did not confer cross-tolerance to LSD and vice versa [40]. There was no great degree of cross-tolerance between the cholinergic blocking type of hallucinogen (scopolamine and JB–318) [36] and LSD. Finally, tolerance to LSD did not confer cross-tolerance to Δ^9- tetrahydrocannabinol, the most active material in marihuana [33].

In a sense, we missed the boat with the hallucinogens of the LSD type. We soon became aware that many of our former addict patients dearly loved the effects of LSD as long as the dose was not too high—less than 2 μg/kg. That was a clear danger signal that abuse of the substances might occur but we did not see how an illicit market could be supplied. In short, we could not predict that "gurus" would arise in the universities who would begin to push LSD and related material, the arrival of the "flower children" of the sixties and the misguided synthetic efforts of graduate students in chemistry who began to make LSD, amphetamines, and other things in that same sad decade.

Marihuana and Tetrahydrocannabinols

In 1964 a small amount of pure Δ^9-tetrahydrocannabinol (Δ^9-THC) and other materials isolated from hashish was supplied to us by Professor Korte and his associates in Bonn, Germany. We found that Δ^9-THC reproduced the effects of "good" marihuana in man both when given orally or when smoked [32]. The symptoms included euphoria, giggling, alteration of time sense, distortions of sensory perception and, in some patients, hallucinations. Patients tolerant to LSD were not cross-tolerant to Δ^9-THC [33]. Objective changes after Δ^9-THC included conjunctival injection and a dose-dependent tachycardia. We were never able to undertake chronic experiments with Δ^9-THC.

Another interesting compound, the 5-dimethylheptyl congener of tetrahydrocannabinol (CA–101 or SKF–5390), was studied in the late 1950's but because the compound was of interest to the armed services the data were never published. The drug, a mixture of isomers, was effective orally (1–2 mg total dose) or by smoking. The subjective effects were recognized by experienced subjects as being similar to those of marihuana except that they appeared more slowly and lasted longer. Subjective effects included euphoria, marked sedation, dry mouth, distortion of time sense, altered sensory perception and, in some cases, anxiety. Objectively, the outstanding effects were tachycardia, postural hypotension leading to fainting on standing and conjunctival injection. Cardiovascular effects persisted at least 48 hours after 2 mg of SKF–5390 orally.

The Concept of Drug Dependence

During the 19 years and more covered by this paper, it became evident that there were many types of compulsive drug use. Some of these—the opiate and barbiturate types—were associated with psychic dependence, tolerance (at least partial), and physical dependence. One—cocaine—was associated with psychic dependence, little or no tolerance (?), and no physical dependence. Others—the hallucinogens and amphetamines—were associated with psychic dependence, high tolerance, and no clear-cut physical dependence. All of these forms of drugtaking had become social problems of varying degrees of importance. The term "addiction" had long been used as being synonymous with physical dependence with resulting confusion. Accordingly, new terminology had to be developed and so the concept of "drug dependence" was formulated by Dr. Nathan Eddy and his collaborators [2] on the WHO Expert Panel on Drug Dependence. In this formulation, psychic dependence is the only necessary characteristic. Tolerance and physical dependence are important but not essential characteristics. The trouble with this formulation is the difficulty in defining psychic dependence and the even greater difficulty in measuring it. We also are very much in the dark about the pharmacological basis of psychic dependence.

So after 40 years and more of research, although our knowledge has increased in almost exponential fashion, we remain more ignorant than we were. But that is always the case with science.

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Dr. H. Fraser, *Associate Director, Addiction Research Center, 1949–63*

Methods for Evaluating the Overall Abuse Liability of Weak Opiatelike Drugs

H. Frank Fraser, M.D.

It has been pointed out that in evaluating a new drug, whether morphine agonist or antagonist, one must consider not only its capacity for inducing physical and psychic dependence, but also its capacity for evoking harm to the individual and/or society. Taking into consideration these parameters, one arrives at an overall abuse potential of a given agent and this should determine the extent to which it would be controlled. It should be realized, however, that we have both "socially acceptable" forms of addiction or abuse, such as alcohol and tobacco, *versus* "socially taboo" forms such as heroin.

Evaluating the abuse liability of weak opiatelike drugs is difficult because the picture is not black or white for in many instances the investigator is exploring a gray area. The public health problem is—do the advantages of the new drug in respect to relieving pain, cough, or diarrhea outweigh its deleterious effects, such as capacity for abuse or some toxic feature.

In thinking about the responsibility of a clinician at the Addiction Research Center, it is thought that he should wear two hats. One hat involves protecting the public and, as a matter of fact, the world, because our findings are accepted by the World Health Organization for the introduction of new drugs which might have dangerous abuse potential without appropriate warning to the public and appropriate controls over sales. The other hat he should wear is one which would attempt to explore drugs which show promise of a lesser abuse potential than those now in clinical use and which are efficacious as analgesics, antitussives, or antidiarrheal drugs.

Our topic today is methods for evaluating the overall abuse liability of weak opiatelike drugs. We cannot discuss this subject without paying a great tribute to Dr. Himmelsbach for the many techniques which he developed for measuring physical dependence. We are indeed honored to have him present with us today. The methods which will be presented were those evolved at the Addiction Research Center from 1949 to 1963 in which the author was personally associated. They were developed in conjunction with Drs. Isbell and Martin in close collaboration with many others on the staff. Much credit should be given to our faithful aides on the ward and the continuous and tremendous cooperation of the patient addicts should be recognized. In connection with all of these methods, advantages will be pointed out, but also insofar as possible, their limitations. This review should not be considered as a comprehensive one covering all methods developed, particularly those of Drs. Hill and Haertzen who evolved specific scales to classify groups of drugs as well as scales to measure euphoria and dysphoria, which will be independently reported by Dr. Haertzen. You will indeed be impressed with the incisiveness and the overall merit of their tests.

Measures for Evaluating the Effects of Opiatelike Drugs 1949–63

1. *Photographic measurements of the pupils.* The pupil and the centimeter ruler were photographed simultaneously after the patients had remained for 15 minutes in complete darkness, using a stroboscopic light, with a flash duration of 1/5,000th of a second [10]. This method has been simplified over the years in that it was found that ordinary light could be used rather than darkness and a Polaroid CU camera has been

substituted for the original camera [23]. The prolonged length of action of *l*-alpha-acetylmethyladol [5], a drug now being used to treat heroin addicts instead of methadone, is compared with that of morphine in figure 1.

The intensity and duration of miotic effects produced by opioids correlate well with other physical dependence-supporting characteristics, the incidence of side reactions, and the intensity of morphinelike euphoria induced. The method is most useful in evaluating single doses of analgesic drugs when it is used in conjunction with other procedures.

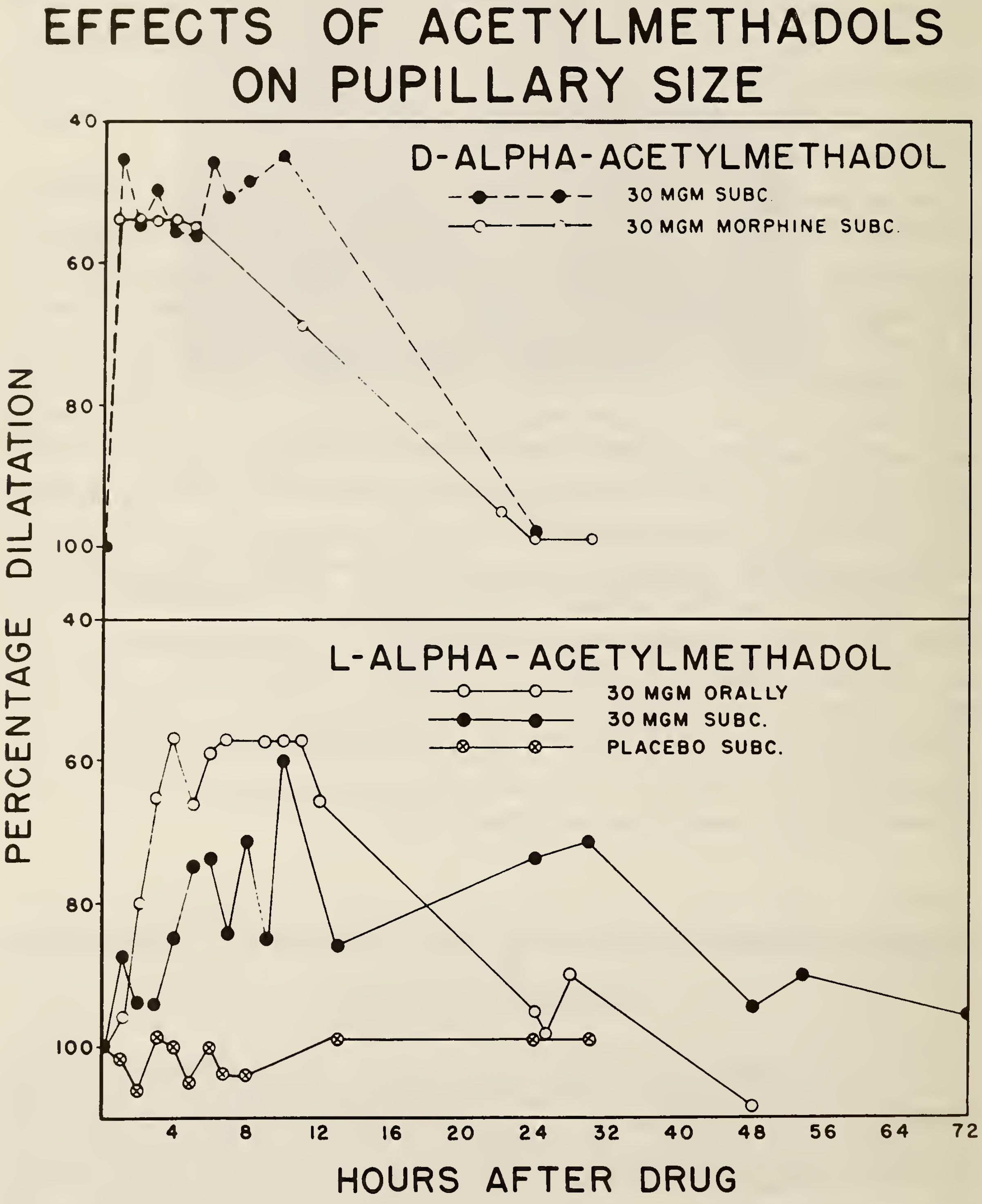

FIGURE 1. *Effects of alpha acetylmethadols on the size of the pupil in one patient as compared to morphine. Reproduced from Fraser and Isbell* [5].

It has also been employed by Fraser et al. [6]and Martin and Fraser [25] in assessing tolerance.

2. *A 24-hour substitution test of opiatelike drugs.* Formerly a single dose of the agent under investigation was given to individuals stabilized on morphine, approximately 240 mg/day. The dose was given 30 hours after abrupt discontinuance of morphine, when the withdrawal syndrome was reaching its peak (Himmelsbach procedure). The subsequent course of abstinence intensity was compared with that to be expected in otherwise untreated individuals. A more adequate procedure has since been devised—a procedure that can be repeated on the same individual at weekly intervals because the abstinence syndrome is never allowed to reach a seriously disturbing intensity. Thus double-blind cross-over observations can be made comparing, in the same individual, one or more dose levels of one or more experimental agents, a placebo and a standard dose of morphine [8]. In fact by using two or more doses of the standard (morphine) and two or more doses of the unknown relative potencies can be ascertained respecting substitution capacity [8].

A group of 5 to 12 individuals is given morphine subcutaneously regularly, the dose being built up rapidly to 240 mg/day and stabilized at the level for not less than 30 days. Beginning with the evening dose (10 p.m.) and continuing through 24 hours, a coded substance (experimental drug, placebo, or standard morphine dose given as an unknown) is administered in place of the regular morphine doses. Beginning the next morning, 14 hours after the last regular dose of morphine, observations are made at regular intervals, recorded and evaluated according to the Himmelsbach [17] hourly score for abstinence phenomena. The substitution procedure is repeated at weekly intervals until each individual has received in random order at least one dose level of the experimental drug, a saline injection as a placebo, the regular stabilization dose of morphine, and perhaps one or more dose levels of one or more other agents. The mean hourly Himmelsbach score for all patients for each agent is plotted and a comparison is made between the experimental agent and morphine or placebo. If the drug is ineffective as a morphine substitute, the graph of abstinence phenomena intensity will coincide with that obtained after the administration of a placebo. If it is morphinelike in some degree, the graph of abstinence scores observed will approximate that obtained after continuation of morphine as an unknown during the substitution period or will fall between the placebo and morphine scores, depending upon the effectiveness of the dose used as a morphine substitute. A more direct and perhaps simpler comparison is obtained by summing for each agent for each individual the hourly point scores and calculating the mean total abstinence score for 24 hours (TAS–24). This score will be high (150 or more) for placebo substitution or low (3 to 8) for complete morphine substitution (figure 2).

The limitation of the 24-hour substitution technique is its inability to predict the degree of physical dependence of the unknown that will be demonstrated when it is administered in a prolonged substitution [16] test or in a direct addiction test and when withdrawn abruptly, i.e., overall abuse liability (figure 3).

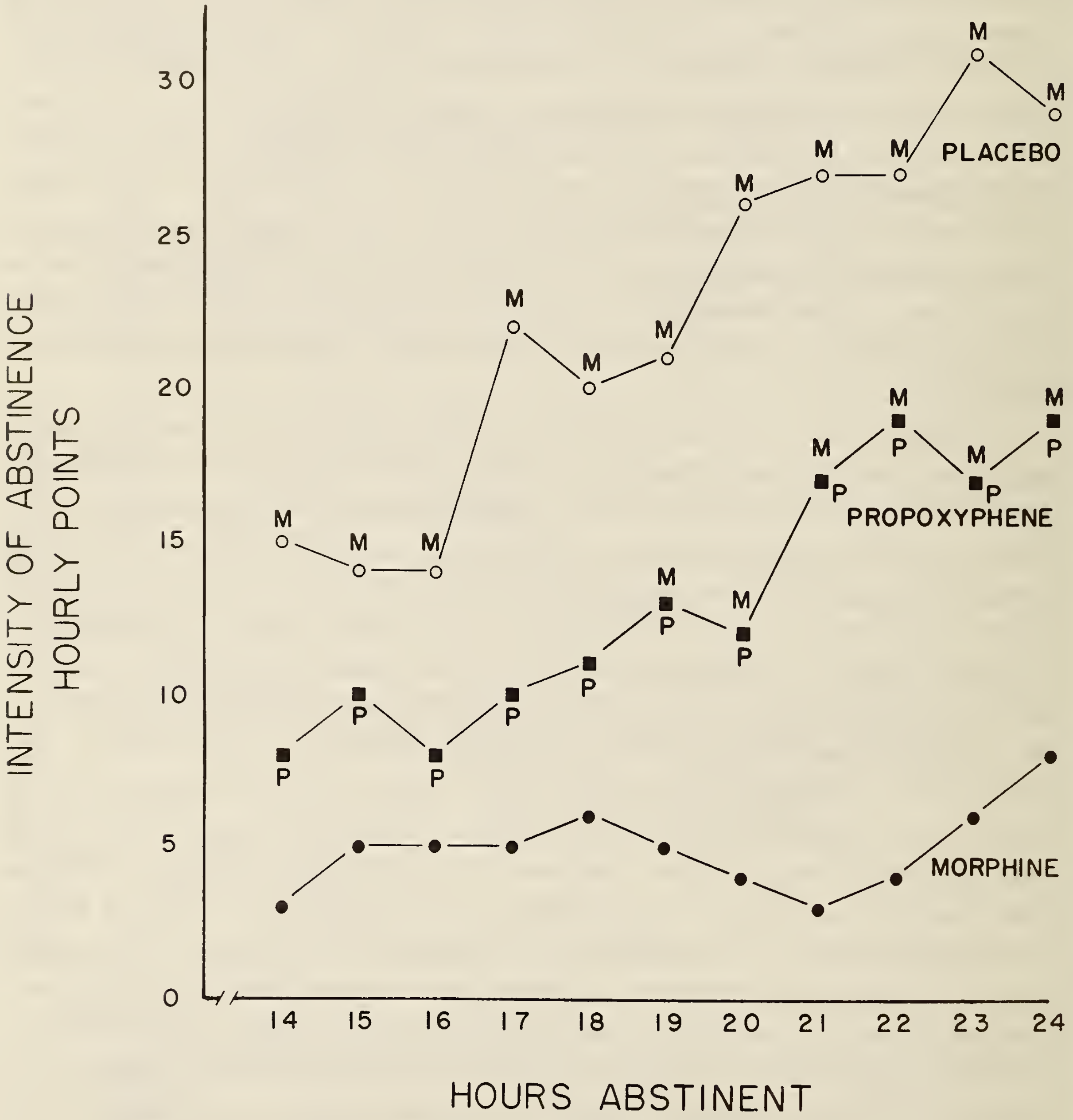

Figure 2. *Substitution of propoxyphene for morphine for 24 hours. The figure compares the intensity of abstinence when propoxyphene was substituted orally for morphine (1) with that observed when a placebo was substituted, and (2) with that observed when the regular dose of morphine was continued. Each point on the placebo and propoxyphene curves represents the average scores of the same 11 subjects. Each point on the morphine curve represents the average score of 9 of these 11 subjects. The letter P signifies that the point is significantly different from the corresponding point for the placebo; M signifies that the point is significantly different from the corresponding point for morphine, indicating some suppressive effect on abstinence from morphine. Reproduced from Fraser and Isbell* [7].

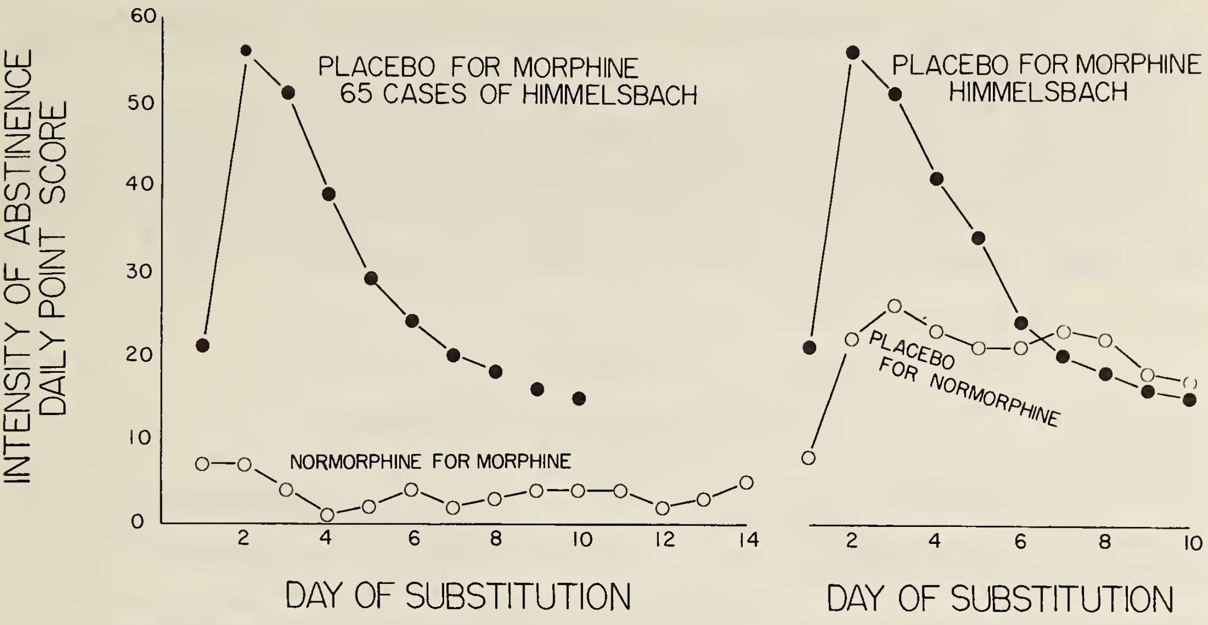

FIGURE 3. *Substitution of normorphine for morphine. Curves with solid circles in both left- and right-hand portions of the graph represent intensity of the illness (abstinence) which follows withdrawal of morphine, and is taken from data of Kolb and Himmelsbach* [21]. *Open circles show the results after substitution of normorphine for morphine (left section), and after substitution of placebo capsules (withdrawal) for normorphine. Reproduced from Fraser et al.* [16].

3. *The single dose opiate questionnaire.* When one surveys the opiates to which persons become addicted in the United States, there is a predominence of addiction to heroin, and one is struck by disparity in the incidence of addiction to various opiatelike drugs. For example, although codeine accounts for at least 80 percent of the natural opiates sold on prescription and is available to the public in limited amounts in mixtures (exempted preparations), the incidence of addiction to codeine is much less than that to morphine. Also, when opium is available in limited quantity in oral preparations of low morphine content, such as paregoric, the incidence of addiction is low. These observations by the U.S. Bureau of Narcotics [27] have been confirmed by the incidence of addiction to various opiatelike drugs as revealed by histories of patients admitted to the hospital in Lexington, Ky. [28]. It was thought, therefore, that addicts definitely discriminate between drugs, and that preference for certain drugs and routes of administration, apart from factors of availability, might be demonstrated in an experimental setting. Experiments were set up for evaluating quantitatively the attitude of opiate addicts toward opiates or opioids when they were administered in single or chronic dosage schedules [14].

Such an approach should be considered a complement to Himmelsbach's physical dependence quantitative evaluations. In other words, it was thought that there must be something about narcotics and other drugs that addicts like before they actually become dependent on them. And as a matter of fact, physical dependence is not an essential feature of abuse, witness cocaine and amphetamine.

The single dose questionnaire for opiates (patients' and aides' ratings) is shown in table 1.

All responses to all items of the questionnaires were tabulated, but for presentation, responses relating to the effects of the drugs and a placebo were classified under the headings: (1) feel medication, (2) identification as "dope" (opiates), (3) score of opiate symptoms or signs, and (4)

TABLE 1

Items of Single-Dose Questionnaire

Subject rating	Observer rating
1. Do you feel the medicine? Yes	Any evidence of drug effect? Yes
No	No
2. Behavior is most like what drug listed below (check 1):	Behavior is like that seen after:
a. Blank	a. Blank
b. "Dope"	b. "Dope" (opiate or potent synthetic analgesic)
c. Cocaine	c. Cocaine
d. Marihuana	d. Marihuana
e. "Goofballs"	e. "Goofballs"
f. Benzedrine ("Benny")	f. Benzedrine ("Benny")
g. Other	g. Other
3. Check each of the sensations which you feel:	Check each item which you think the patient shows:
a. Normal (no change)	a. Normal
b. Turning of stomach (1)*	b. Scratching (2)
c. Skin itchy (2)	c. Red eyes (1)
d. Relaxed (1)	d. Relaxed (1)
e. "Coasting" (2)	e. "Coasting" (2)
f. "Soapbox" (1)	f. "Soapbox" (1)
g. Pleasant sick (1)	g. Vomiting (1)
h. Drive (2)	h. Nodding (2)
i. Sleepy (1)	i. Sleepy (1)
j. Nervous (1)	j. Nervous (1)
k. Drunken (1)	k. Drunken (1)
l. Other	l. Other
4. My liking for this drug is most nearly described by which of the following:	How much do you think the patient liked the effects of this drug?
a. Not at all (0)	a. Not at all (0)
b. Slight (1)	b. Slight (1)
c. Moderate (2)	c. Moderate (2)
d. A lot (3)	d. A lot (3)
e. An awful lot (4)	e. An awful lot (4)
f. Other	f. Other

* The figures in parentheses following items in questions 3 and 4 are the weights given to the particular responses for calculating the opiate symptom, opiate sign, subject's "liking" and observer's "liking" scores. Reproduced from Martin [24].

"liking" score. Each of these parameters was separately tabulated for patients and aides, and curves of mean time course responses or rating scale scores were constructed. In addition, a total response score (TRS) was computed separately for patients and aides for each parameter by adding all the responses or scores recorded subsequent to drug or placebo administration. This TRS score for each parameter approximates the area under the time-action curve and these values were used for making statistical comparisons between drugs and doses by the paired "t" test [2] and for calculating dose-response curves.

The reports of patients for an unknown drug I–K–1 which exhibited practically no morphinelike effects is compared with those of 300 and 600 mg of *d*-propoxyphene and a placebo (figure 4). Concurrent observations of pupillary diameter were also made. Satisfactory dose response curves are exhibited for *d*-propoxyphene for all parameters. Measurements of pupillary diameter follow a corresponding course (figure 4). This study was double blind.

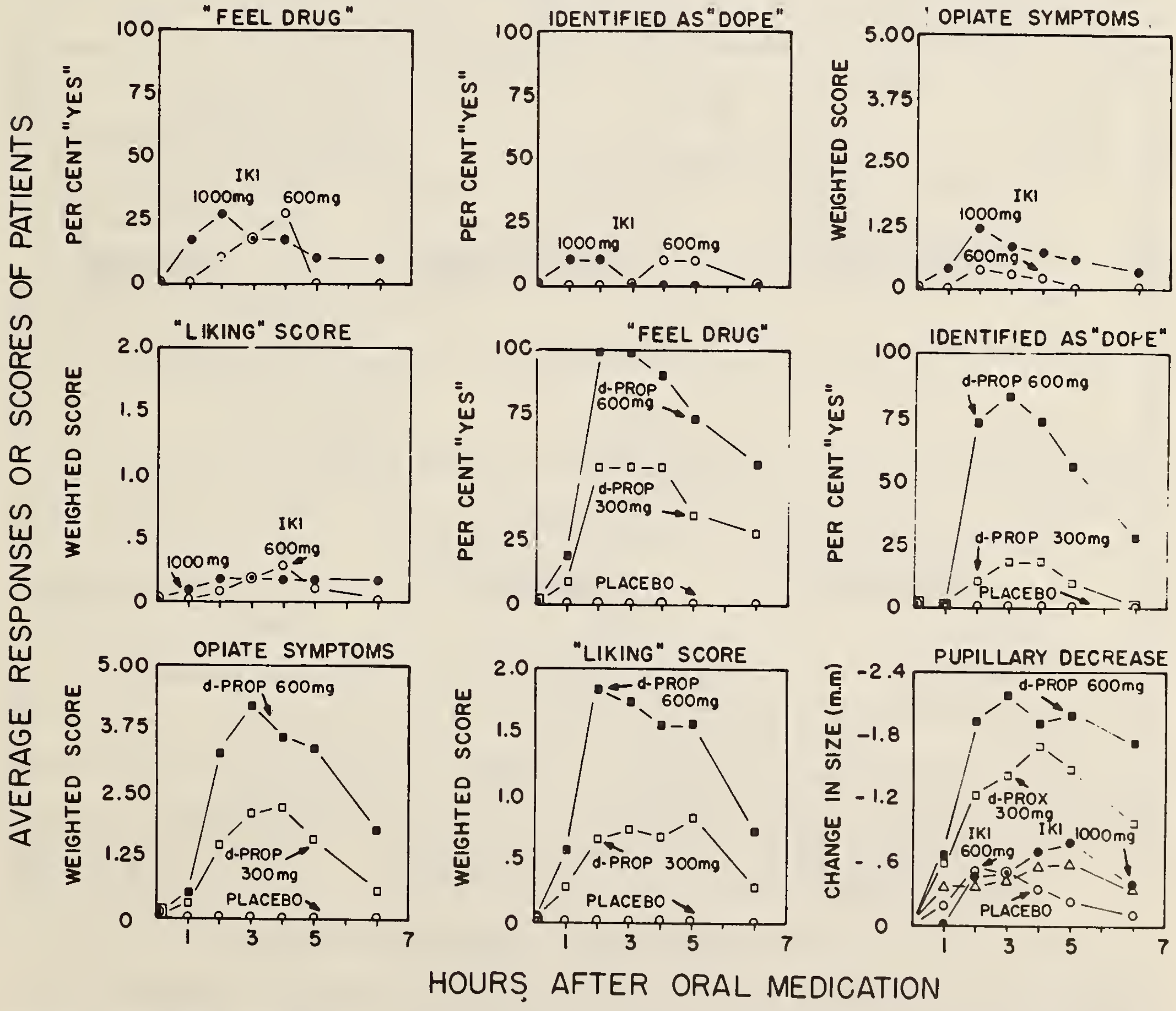

FIGURE 4. *Single oral doses of I-K-1, d-propoxyphene and a placebo. Comparison of the average ratings of patients, using the single dose attitude questionnaire for opiates for the measurements "feel drug," identification as "dope," "opiate symptoms," and "liking" score with the changes in pupillary diameter. Each point on each curve represents an average of data obtained on 11 men, each of whom had each medication orally. Reproduced from Fraser et al.* [14].

The reports of patients and aides are illustrated in figure 5 for codeine, R–1132 (diphenoxylate or Lomotil) and a placebo. The curves show parallel responses for patients and aides (observers) except that the aides give a higher rating for morphinelike effects than the patients. The more rapid onset of effects for codeine as compared to R1132 (diphenoxylate) shows for all parameters measured.

4. *A short direct addiction technique and the chronic opiate questionnaire.* It has long been realized that the direct addiction technique most closely simulates the abuse pattern of addicts, but this procedure was used infrequently in testing drugs for addiction liability because it was previously thought that drugs had to be given in high dosage for 30 to 180 days in order to develop a significant degree of physical dependence. If a "short" addiction technique (18 to 20 days) could be developed it would

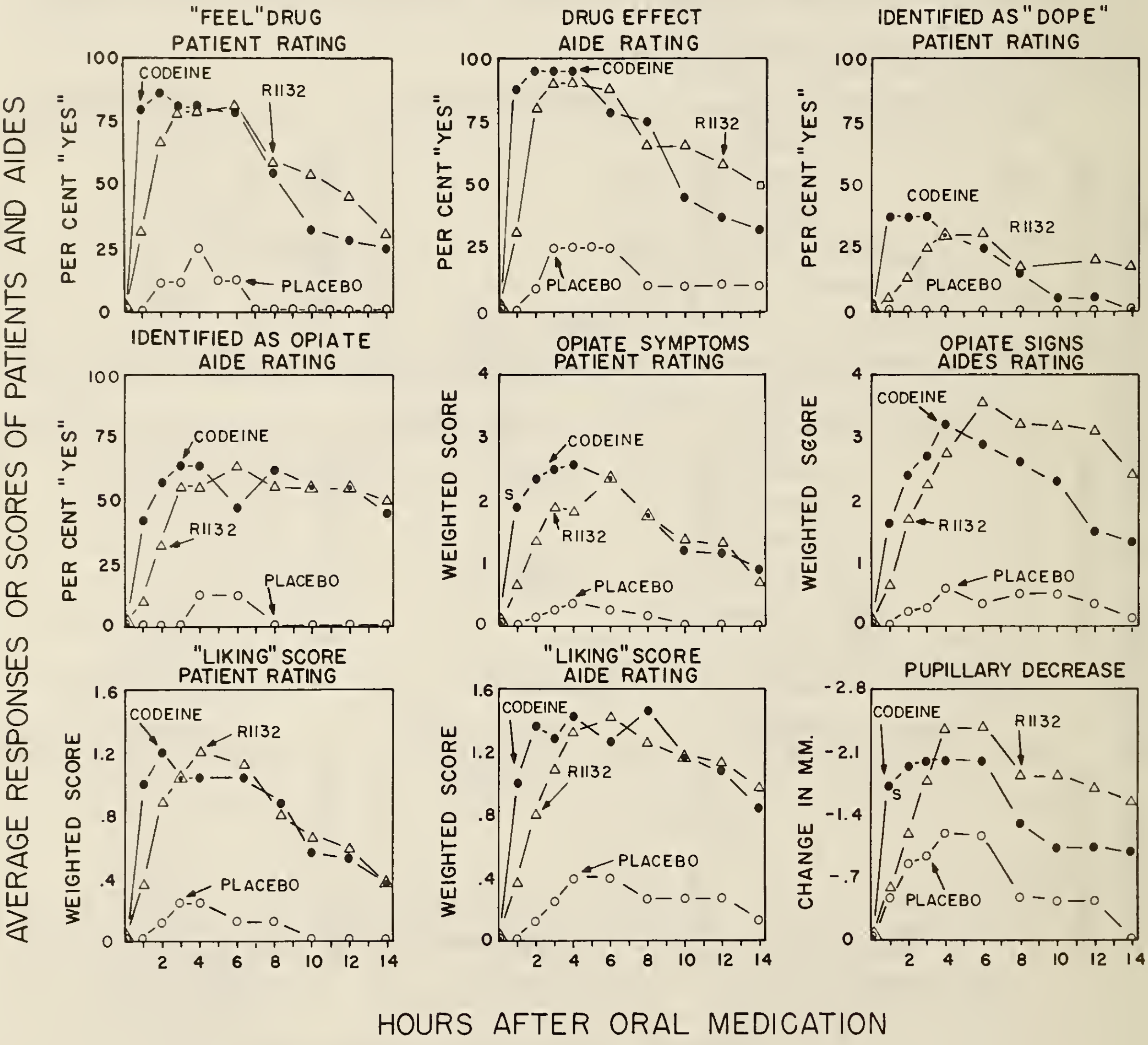

FIGURE 5. *Single intravenous doses of I-K-1, d-propoxyphene, codeine, and a placebo. Comparison of the average ratings of patients, using the single dose attitude questionnaire for opiates for the measurements "feel drug," identification as "dope," "opiate symptoms," and "liking" score with the changes in pupillary diameter. Each point on each curve represents an average of data obtained on 16 men, each of whom had each medication intravenously. Reproduced from Fraser et al.* [14].

be advantageous from the viewpoint of economy of patient days and would more readily permit the use of a "double-blind" technique—employing a standard drug, such as morphine, against which drugs of unknown addiction liability could be compared in the same individual. Experiments were therefore designed to ascertain the degree of physical dependence which would develop, using a short-term addiction procedure [14].

Since the chronic opiate questionnaire was used during the experiment evaluating the short direct addiction technique these methods have been combined for convenience [14].

Eight persons served in this experiment which had the following objects:

1. Could a "short" direct addiction test employing morphine, codeine, and a placebo as standards for comparison be used to assess the addictiveness of new drugs?
2. Would patients in such an experiment differentiate subjectively between a placebo and active drug, and between active drugs of varying types and potencies, and could aides from their observations make similar differentiations?
3. How well would patients and aides agree in their interpretations of drug effects?
4. How well would patients and aides detect the substitution of a placebo for an active drug?
5. Would physical dependence of measurable degree develop in the course of 18 to 20 days?

Assuming that significant but varying degrees of physical dependence did develop on the seven drugs, how well would the questionnaire ratings of patients and aides, which were obtained during addiction, correlate with objective measurements of abstinence obtained after withdrawal?

Patients received the medications listed in table 2 in randomized order for periods varying from 18 to 20 days. All drugs were administered in four approximately equal doses on a double-blind basis and withdrawn by substituting placebo capsules or injections, depending on the particular drug being given. Withdrawal periods lasted 10 days, after which the patient began another round of chronic drug administration.

The "attitude" of the patients toward the various drugs was ascertained daily at 7 p.m. from their responses to the chronic dosage questionnaire for opiates, using the ratings of subjects and observers. Throughout the study, rectal temperature, pupillary size, pulse and respiratory rates, and blood pressure were measured routinely three times daily. Patients were weighed daily at 6 a.m.

In order that the reader may relate the "attitude" toward drugs as

TABLE 2

The starting and maximum daily dose (mg) of each drug used in the direct addiction test, Experiment 4.

In addition, the doses used are related to an equivalent initial and maximum dose based on the potency of each drug in suppressing abstinence from morphine.

Drug	Actual daily dosage		Equivalent dosage to morphine			Toxic signs and symptoms that usually limited acceleration of dosage above those attained
	Starting	Maximum	Potency ratio	Starting daily dose	Maximum daily dose	
Morphine, s.c.	32	240	1	32	240	
Morphine, orally	32	240	2.86	91	686	Respiratory depression and sedation
Codeine, orally	200	1,500	14.7	470	3,530	Constipation, pruritus, difficulty in urination, respiratory depression, and sedation
Phenazocine, s.c.*	4.8	12–36	0.12	3.84	28.8	Respiratory depression, headache, sedation
Levophenacylmorphan*	4–4.8	24–36	0.11	3.52	26.4	Nausea, nervousness, depression
R–1132†	40–64	160–480	1.8	57.6	432	Excessive sedation
NIH–7296A‡	180	1,200	24.3	777	5,830	Headache, dizziness, palpitation, and nervousness

* See Fraser, H.F. and Isbell, H. [8].
† Diphenoxylate; see Fraser, H.F. and Isbell, H. [9].
‡ d-3-Methoxy-N-phenethylmorphinan.

rated by patients and observers to physiological changes, the effects of all drugs and a placebo during the first 18 days of administration on several measurements are described. As compared to a placebo, no drug significantly affected systolic blood pressure, rectal temperature, hours of sleep or "hours of activity" (time spent off ward). All drugs significantly decreased the average daily respiratory rate as compared to a placebo. The average daily respiratory rates were as follows: placebo, 18.8; morphine subcutaneously, 13.8; morphine orally, 15.1; phenazocine subcutaneously, 14.8; levophenacylmorphan subcutaneously, 14.0; R–1132 orally, 14.6; codeine orally, 14.5; and NIH–7296–A orally, 16.1. Hours of "inactivity" (per 24 hours lying horizontal on the bed, whether sleeping or not) were significantly affected by only one drug, R–1132, since the average was 12.50 hours daily as compared with 10.35 hours for a placebo. (All above statistical comparisons were made by the paired test using each individual as his own control.)

The extent to which drugs, including a placebo, were identified as "dope" or opiates by patients and aides is illustrated in figure 6. In the case of the potent opiates, there is quite good agreement between patients and aides respecting the extent to which the drugs were identified as being opiatelike, but for the less potent drugs (codeine, R–1132 and NIH–7296A), there is considerable discordance between reports of patients and observations of aides; in fact, the aides rated codeine orally almost as high as morphine subcutaneously. It is remarkable, since the study was conducted "double-blind," that in no instance did the patients state a placebo produced a drug effect. Likewise the aides made exceptionally few errors in this respect.

An estimate of the "strength" or potency, using a scale graded from 0 to 7, shows that the aides rated the potency considerably higher than did the patients (figure 6). Again it is noteworthy that neither patients nor aides attributed any particular potency to the placebo (figure 6).

In response to the question "Would you like to take this drug every day?" there is radical difference between the answers of patients and aides (figure 6). It was surprising to the experimenters that only 38 percent of the patients indicated they would like to take subcutaneously administered morphine daily. This low incidence of acceptance of morphine is consistent with observations of Lasagna et al. [22] and may be due in part to the fact that the American addict is accustomed to taking his drugs intravenously and the latter route is his standard of reference [25]. When 15 patients who had received morphine chronically in this and other "attitude" tests were asked to name their drug of first, second, and third choice, none named morphine as first, and only two named morphine as their second choice. The low regard for all of these drugs when administered orally is readily apparent (figure 6). Patients discriminated among drugs to a high degree, but

NIDA Addiction

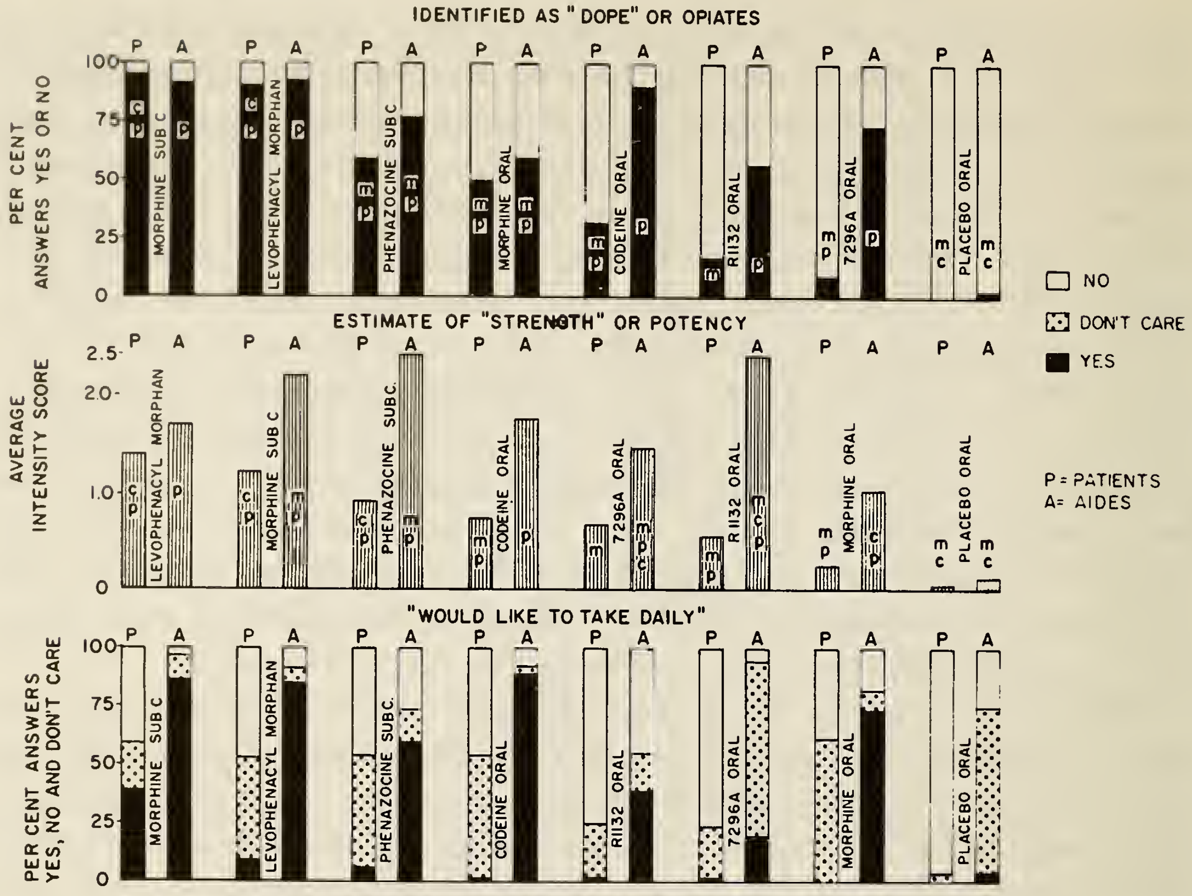

FIGURE 6. *Comparison of average ratings of patients and aides using the chronic dosage questionnaire for opiates in a "short" addiction test of 18 to 20 days involving seven drugs and a placebo.*

The variables measured included: identification as "dope" or an opiate, "strength" or potency, and "would like to take the drug daily." Statistical comparisons by the paired "t" test among drugs respecting identification as "dope" or opiate, and "strength" or potency are summarized separately for patients and aides. A significant difference (p <0.05) between morphine subcutaneously and other drugs including a placebo is shown by the symbol "M"; between codeine orally and other drugs, by the symbol "C"; and between a placebo orally and other drugs, by the symbol "p." Reproduced from Fraser et al. [14].

the aides showed much less discrimination and rated them very similarly (figure 6). For example, morphine subcutaneously was rated similar to codeine orally by the aides.

In the case of patients, there is evidence that their responses to the three questions, identification as "dope," "strength," and "would like to take daily," are to some extent measuring a common component since all three show a significant rank order correlation (P<0.05). On the other hand, in the case of observers, the correlation was significant only between identification as "opiate" and "would like to take daily."

The above ratings of patients (figure 6), obtained during addiction, for the seven drugs and a placebo were tested for rank-order correlation with the degree of physical dependence manifested during the 10 days of withdrawal (average area under the curves, figure 6). The correlation of abstinence scores with identification as "dope" was 0.98, with potency, 0.75, and with "would like to take daily," 0.83; all are significant

($P<0.05$). The extremely high correlation between the subjective measurement of "dope" on the part of the patients and the observed measurement of abstinence by the aides is noteworthy. In the case of the aides, none of the correlations for these parameters with intensity of abstinence was statistically significant, but in the case of identification as an opiate the correlation of 0.74 approximated significance.

Ratings of patients correlated with those of aides only in the parameter "identification as an opiate" ($P<0.05$).

It is evident from the responses of patients and aides to their respective chronic dosage questionnaires that patients discriminated among drugs to a high degree, but the aides rated many of them very similarly. For example, morphine subcutaneously and codeine orally were given equivalent ratings by the aides. It is apparent that patients have "private" and probably different criteria for rating which are not available to the observer. For example, in contrast to the aides, patients evidently were quite unimpressed by such effects as miosis, hypnosis, and respiratory depression. Both patients and aides made reliable responses in the sense that the responses of both may be repeated for the same drug in another experiment using other patients: for example, where this experiment was repeated in the case of morphine and a placebo. But the predictiveness of responses of both aides and patients regarding the abuse liability of any drug must await further studies of "attitude," with more subjects, additional drugs, and utilizing, insofar as possible, intravenous administration. In part this has been accomplished in other experiments [8, 23]. (Martin and his collaborators [26] have introduced a modification of the chronic dosage questionnaire adding the concept "do you 'dislike' the drug?" This is considered an improvement.)

One could interpret the lower acceptance of oral drugs in these tests as a general protest on the part of the patients for orally administered drugs. However, this is not necessarily so since methadone orally given over a 19-day interval was highly accepted (table 3). Furthermore, Jasinski and Nutt [20] found the reverse of these findings when morphine alone was compared with morphine plus amphetamine. They observed higher acceptance by patients than by the observers. Since amphetamine counteracts to a considerable extent miosis, fall in body temperature, and decrease in respiratory rate the aides interpreted the combination as a weaker drug, whereas the patients were impressed by the euphoria and considered the combination more potent. So again it is demonstrated that both patients and observers are making reliable observations but are interpreting different phenomena.

The degree of physical dependence as computed by the "standard" and "modified" Himmelsbach procedures on the seven drugs and placebo, when the latter was considered to be the "drug of addiction," are shown in figure 7. It is apparent that in the case of morphine both

TABLE 3

Response of patients and observers† to the question, "do you like its (Methadone) effects" during first 19 days of addictive schedule *

Question	Patients N=6**	Observers
"Dislike"	7	1
"Don't Care Either Way"	11	6
"Slightly"	35	4
"Moderately"	27	25
"A Lot"	34	78

* There were a total of 114 responses by patients and a similar number for observers.

** One patient appeared to have skipped over this question for 9 days. His response for 9 additional days past the 19th day were used and the observer's response for those additional days was used also.

† Computed by Fraser from unpublished data of Martin et al. [26].

orally and subcutaneously, levophenacylmorphan, phenazocine, codeine, and R–1132, significant degrees of physical dependence developed under the conditions of these experiments. It is also evident that there is a relatively constant disparity between scores computed, using the last 7 days on the drug as a baseline (Himmelsbach) and the 30 days on a placebo as a baseline (Himmelsbach modified). All of the latter measurements were statistically different except when the placebo was compared by the two methods.

Thus, for these drugs the 18 to 20 day direct addiction test induced an anticipated degree of dependence which satisfactorily differentiates among drugs. In addition to these drugs, the "short" addiction test has been evaluated on morphine and heroin intravenously, heroin subcutaneously and 1-(beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitaobenzimidazole methanesulfate (NIH–7607). The results were as anticipated.

The Himmelsbach "modified" score is based on the placebo baseline and is considered the most reliable since it contains less artefact.

5. *The one week intravenous direct addiction test.* This is an intravenous procedure which is to be employed only after all drugs involved have been tested completely in single doses to determine their potency and after substitution tests have been conducted [11]. A typical experiment employing this technique is described as follows: In a single-blind study six subjects received drugs intravenously and one subcutaneously because all of his superficial veins were sclerosed. A "sample" of a high dose of each drug was given at 3-day intervals—180 mg of I–K–1 (1-(p-chlorophenethyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline), 180 mg of *d*-propoxyphene, 120 mg of codeine, and 30 mg of morphine—in randomized order. (The amount of the single dose was determined on the basis of previous experimental tests.) Each pa-

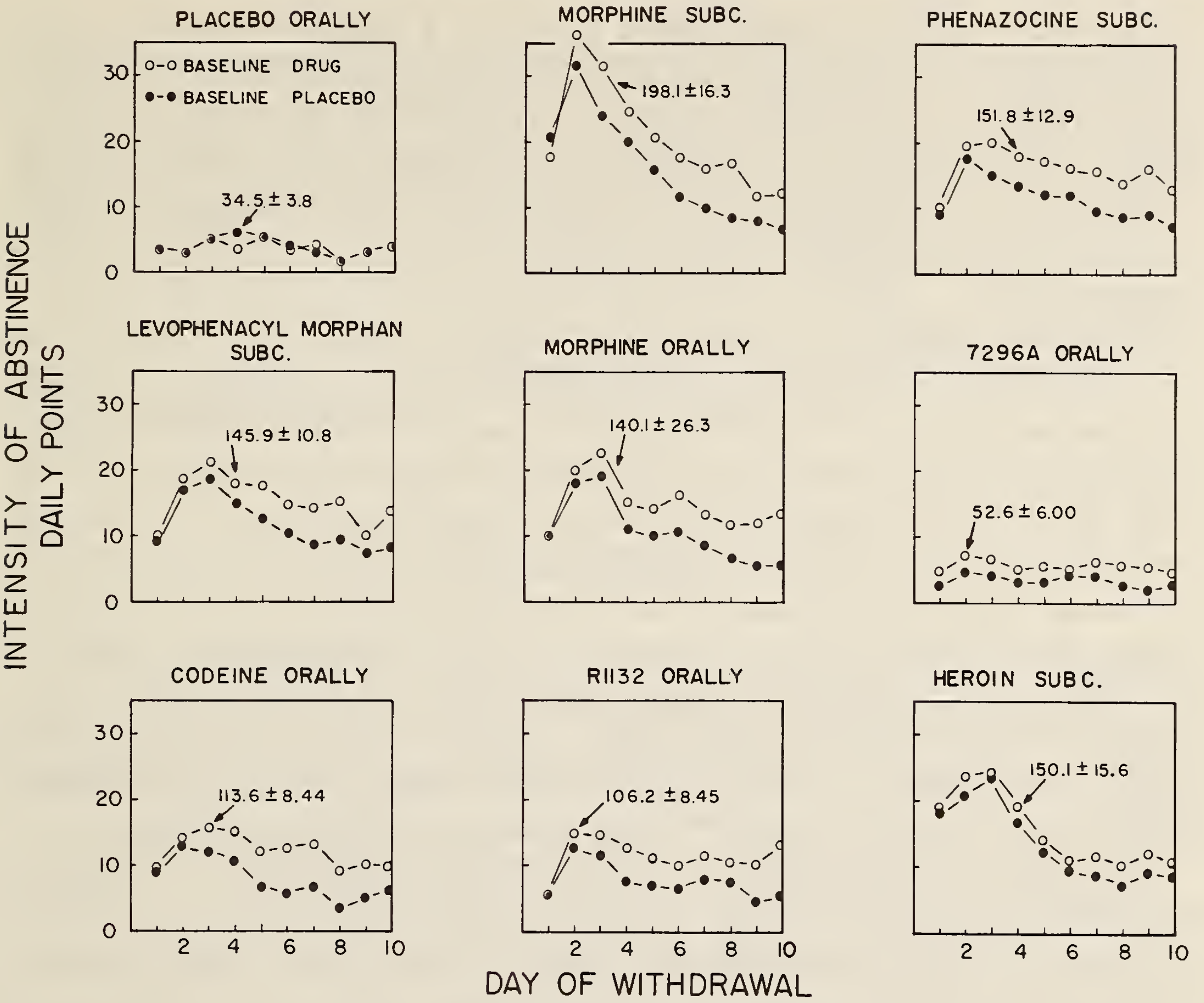

FIGURE 7. *Comparison of average intensity of abstinence for 10 days after abrupt withdrawal of eight drugs and a placebo, each of which was administered for 18 to 20 days (see text explaining the two methods for computing abstinence scores).*

The numbers in each individual graph represent the mean area scores ± the standard error under the time-action curves, using "standard" scores, i.e., those derived from the drug baseline. All of the latter scores were significantly different from those of a placebo when the latter was considered to be the drug of addiction, by the paired "t" test. For the "modified" scores, all were significantly different from a placebo except NIH–7296A. It is apparent that potent and even moderately potent opiatelike drugs induce significant degrees of physical dependence, even though the interval of addiction is quite short. The placebo and all drugs except heroin were compared in the same subjects. The method was sufficiently sensitive to show significantly greater abstinence following withdrawal of morphine than after withdrawal of phenazocine and levophenacylmorphan. Subcutaneously administered heroin and morphine were evaluated in eight different subjects; although the intensity of abstinence following withdrawal of morphine in this study is not illustrated, it was similar to that shown for heroin. Reproduced from Fraser et al. [14].

tient rated each of these drugs on the single-dose attitude questionnaire described previously. After each had received all four sample doses, he was asked to review his response to each on the questionnaire and to rate them in order of preference, 1 to 4. In this preferential ballot morphine ranked first, *d*-propoxyphene second, and codeine and I–K–1 equal and last.

It was explained to each subject that he would then receive for 7 days, in randomized order, all the sample drugs which he elected to take in increasing doses with a withdrawal period of 3 days between each drug phase. However, after his rating of the single doses, a subject could elect not to take any of them during the 7-day phase, to take one or more of them, or after starting any particular drug to stop at any time during the 7 days, go on to the next drug, or discontinue entirely without penalty. At the end each subject was asked again to rate the drugs in order of preference.

The daily amounts of the drugs were as follows: for I–K–1 and *d*-propoxyphene, 360 mg (divided into three equal doses) on the first and second days and 480, 600, 600, 720, and 720 mg (divided into four equal doses) on the third to seventh days; for morphine, 60, 60, 80, 100, 100, 120, and 120 mg (divided into four equal doses); and for codeine, 240, 240, 320, 400, 400, 480, and 480 mg (divided into four equal doses). All drugs were administered intravenously (with the one exception noted above) slowly over a 2-minute interval. Nalorphine (3 mg) or a placebo, on a randomized double-blind basis, was injected subcutaneously at 9 a.m., that is, 3 hours after the last dose of an experimental drug, on the sixth or seventh day of the test. Observations for abstinence signs were made also on the 3 days between drug administrations.

Morphine was definitely the preferred drug in this series; it was taken by all the subjects, however, one discontinued it on the second day because of nausea. *d*-Propoxyphene was taken by all the subjects and by two of them for the whole period of 7 days; the average duration of administration for all subjects was 5.3 days. Even though five men identified the drug as "dope," five discontinued *d*-propoxyphene for such reasons as pain at the site of injection, nausea, loss of appetite, dizziness, and nervousness. One patient took *d*-propoxyphene intravenously for 7 days, but his veins became progressively occluded; successive injections of the higher doses had to be given in different veins and as much as 45 minutes was spent locating a suitable vein. As to codeine, two patients elected not to start the 7-day course of addiction and only three completed the course. After taking the "sample" dose one patient complained that it was "mother-in-law medicine." Those taking codeine intravenously complained that all they felt was a temporary pins-and-needles sensation. Although all the subjects elected to take I–K–1 for the 7 days, it was feasible to administer it to only two subjects (for 2.5 and 6.3 days, respectively) because it induced severe phlebitis and venous thrombosis. All patients complained that with I–K–1 morphinelike effects were absent or very weak and there was pain at the site of injection.

The short-term direct addiction technique has the following advantages: The program is less rigid in design than in the original long-term technique and permits the former addicts to make elections among drugs and on how long they wish to take an agent before trying another.

Furthermore, as indicated above, it brings out rapidly differences among drugs respecting the quality of the subjective effects and characteristics of a drug which determine its suitability for intravenous administration—for example, its solubility and its local irritant and/or thrombotic properties. The primary deficiency of the method is that it does not evaluate adequately the degree of physical dependence. It does, however, give valuable information on the subject's immediate like or dislike of a drug by his usually preferred route of administration and, hence, on whether or not he would be inclined to use it intravenously if it were available to him.

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Discussion

The high degree of acceptance of propoxyphene and codeine in single doses is in marked contrast to the extent to which these drugs were accepted in the intravenous direct-addiction test. Codeine, for example, was classified as "mother-in-law medicine" and two of seven patients elected not to take the subsequent direct addiction test. Likewise, although all seven addicts elected to take propoxyphene intravenously, only two took it for 7 days—complaining of pain at the site of injection, nervousness, and not the right kind of "high." From these results it is apparent, as Fraser [3] and Martin [24] have emphasized, that for many weak opiatelike drugs it may be necessary to perform not only single-dose tests, but also substitution and direct addiction tests in order to properly assess the overall addictiveness of many weak opiatelike drugs. In addition, it may be necessary to administer such an unknown drug by different routes, for example, intravenously as well as orally. Since the direct-addiction test best simulates the abuse pattern of addicts probably more emphasis should be placed on the short-addiction procedures of Fraser et al. herein described [11, 14].

We are now ready to assess the effectiveness, from a public health point of view, of our methodology and our clinical program to evaluate weak opiate drugs. First, in the 40 years of its operation beginning with Himmelsbach there have been no apparent errors in NIDA–ARC recommendations in describing the abuse capacity of opiatelike drugs. With respect to our second public health function, i.e., identifying drugs that will be clinically effective yet will have definitely less abuse liability than the drug it replaces, NIDA–ARC has been very successful with regard to drugs to relieve mild-to-moderate pain, cough, and diarrhea (table 4). These are not ideal drugs for these purposes; however, certain of them which are in the range of effectiveness of codeine have been widely accepted by the medical profession. This is important at the

TABLE 4

NIDA–ARC First Demonstrated by Critical Human Experiments the Minimal Abuse Capacity of the Following Marketed Drugs:

Type of drug	Trade name	References
Analgesics		
d-Propoxyphene HCL	Darvon	Fraser and Isbell [7]
Pentazocine	Talwin	Fraser and Rosenberg [13]
Methotrimeprazine	Levoprome	Fraser and Rosenberg [12]
Ethoheptazine	Zacterine	Fraser and Isbell [4]
Antitussives		
Dextromethorphan	Pertussin	Isbell and Fraser [19] Fraser and Isbell [4]
l-Propoxyphene	Novrad	Fraser et al. [7]
Antidiarrheal		
Diphenoxylate	Lomotil	Fraser and Isbell [9]
Miscellaneous		Fraser et al. [9]
Nalorphine	Nalline	Isbell and Fraser [18] Eddy [1] Wikler et al. [29]

present time, since they have in part replaced codeine, which helped in alleviating codeine shortages.

Insofar as NIDA is concerned, the story of nalorphine is interesting. Its usefulness in human therapy was first demonstrated by Fraser et al. [15] for its ability to antagonize opiate poisoning, in the first instance accidental methadone intoxication in which the respiratory rate declined to 3 per minute. Its usefulness in detecting opiate addiction was subsequently suggested by Dr. Eddy and has been described by Wikler et al. [29]. The low-abuse capacity of dextromethorphan was observed by Isbell and Fraser [19] and Fraser and Rosenberg [12]. It is an effective antitussive with only isolated reports of abuse, and is marketed in the United States by some 50 companies.

Summary

For the years 1949 to 1963 the author has been involved in the development of several methods for evaluating the overall abuse potential of opiatelike drugs. These included: Photographic measurement of the pupillary diameter, a 24-hour substitution test, single and chronic dosage opiate questionnaires, and two short direct addiction procedures.

The above methods in conjunction with many other techniques employed have made it possible for NIDA–ARC to satisfactorily describe opiatelike drugs so that from a public health point of view no dangerously addicting drugs have been introduced into medicine without appropriate control. In addition NIDA–ARC has searched the entire world for drugs which would perform the same function as codeine in relief of mild to moderate pain, cough, and diarrhea and yet would possess definitely less abuse capacity. Several drugs in the codeine category have been evaluated at the ARC and their minimal abuse capacity demonstrated for the first time by critical experiments in man. This led to their subsequent marketing. Several of these have been widely accepted by the medical profession; this is helpful since there is a worldwide shortage of codeine.

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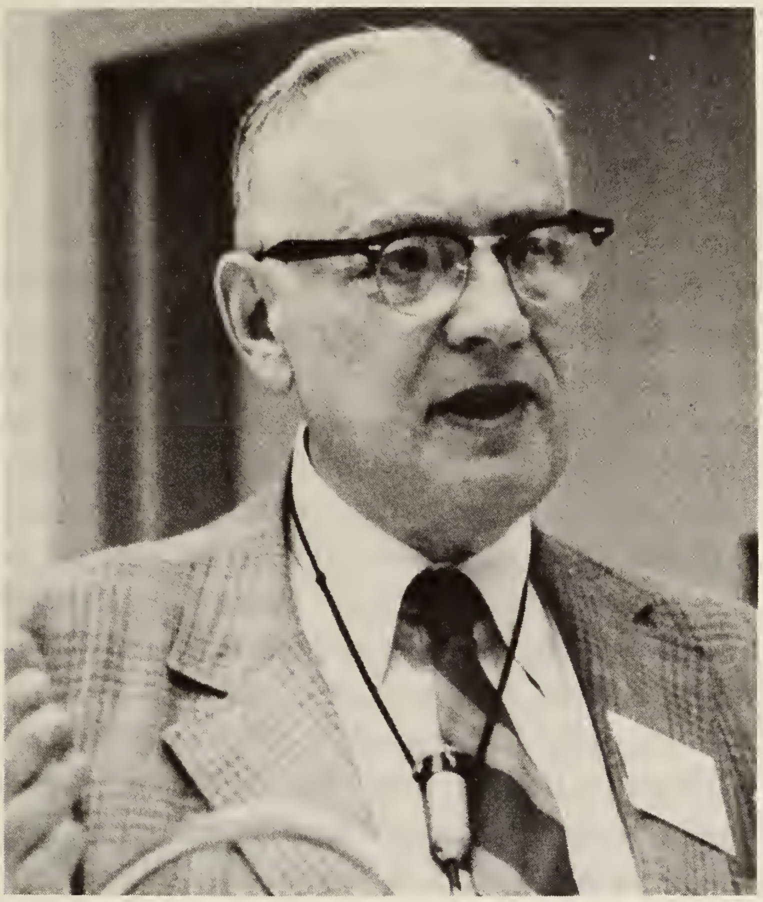

Dr. Abraham Wikler, *Associate Director, Addiction Research Center, 1942–63*

Neurophysiological and Neuropsychiatric Aspects of Opioid Dependence

Abraham Wikler, M.D.

The material in this paper summarizes neurophysiological and neuropsychiatric investigations at the Addiction Research Center selected for their relevance to a "conditioning" theory of opioid dependence and relapse. Because of the thematic nature of this presentation, a strict chronological sequence of the research will not be followed since in actuality, the path of research towards a goal resembles a multiple Y-maze more than a straight runway. Furthermore, a number of studies

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that ended in blind alleys will not even be mentioned. Other neurophysiological and neuropsychiatric research on opioids, barbiturates, alcohol, stimulants, cannabis, and psychotomimetic agents will be reviewed by other contributors to this program.

Among other duties as a resident in psychiatry at the Public Health Service Hospital, 1940–42, I was responsible for the management of the narcotic-withdrawal ward. In those days, addicts were admitted with severe degrees of physical dependence on morphine, heroin, or less frequently, on other opioids, and the only method of narcotic withdrawal was that of "rapid reduction." Needless to say, the withdrawal course was frequently "stormy," and I gained the distinct impression that the intensities of the "storms" were directly related to my presence on the ward or to the addicts' awareness that I was available. Despite the fact that physical dependence on opioids had already been described in animals [19, 24, 35, 36], the question arose whether the opioid-withdrawal syndrome might be at least in part, "psychogenic," especially in man. The difficulty in defining "psychogenic" operationally was solved (rightly or wrongly) by equating this term with "conditionable." Inasmuch as Pavlov had stated [34] that conditioning was not possible in the absence of the cerebral cortex, a partial answer to this question might be furnished by determining whether or not opioid-withdrawal phenomena could be demonstrated in previously decorticated animals. Complementing this line of research would be studies on the conditionability of opioid-withdrawal phenomena in intact animals or man.

An opportunity to carry out such research was afforded by my accession to the staff of the Research Department (later, the NIMH Addiction Research Center) in 1942 in response to an invitation tendered by Dr. C. K. Himmelsbach, Director of Research. First, I spent a year in extramural training in neurophysiology, experimental psychology, and neuropathology at various institutions in Chicago, New Haven, and New York. Several published papers resulted from this training year [3, 38, 46, 48] including one on the effects of single doses of morphine on the intact cat and acutely decorticated, decerebrated, and spinal cats [37]. After my return to the Research Department in Lexington, I commenced the arduous task of preparing long-surviving chronic decorticated and chronic spinal dogs for studies on cycles of morphine (and also methadone) addiction in these animal preparations. Somewhat later, in collaboration with my colleagues, Drs. Harris Hill, Conan Kornetsky, Richard Belleville, Harold Flanary, and others, studies were made on psychological (or conditioning) factors in the actions of single doses of morphine in nontolerant subjects. Still later, with other collaborators, studies were undertaken on the conditionability of the morphine-abstinence syndrome and its relation to relapse. As already stated, the order of presentation of these investigations does not necessarily follow a chronological sequence.

I. Conditioning Factors in Morphine Analgesia

Using the Wolff-Hardy-Goodell radiant heat method, Andrews [1] found that while the "pain threshold" of postaddicts was within the range reported by Hardy, Wolff, and Goodell [9] for normal subjects, single analgesic doses of morphine had no significant effect on this threshold in postaddicts. This surprising finding was confirmed by Isbell and Frank [20] who also found that single analgesic doses of morphine had no consistent effect on "pain thresholds" in response to electrical stimulation of a tooth pulp (through a silver-amalgam filling). Considering these negative findings and the statements of some of the subjects who participated in the tooth-pulp stimulation experiments to the effect that after morphine they still "felt" the pain but "didn't give a damn about it," Hill et al. [13, 15, 16, 17] hypothesized that morphine exerts its analgesic effects not through impairment of any sensory-discriminative functions, but through reduction of what Hardy, Wolff, and Goodell [9] had called the "alarm reaction" to noxious stimulation; furthermore, they hypothesized that such an "alarm reaction" could be "anticipatory" (i.e., conditioned) and that morphine would reduce "anxiety associated with anticipation of pain." To test this hypothesis, a series of studies was carried out on "postaddicts," which yielded the following data: (a) morphine (15 mg s.c.) reduced overestimation errors in judging the relative intensities of brief, painful electrical shocks to the hand under conditions designed to maximize "anxiety," but had no effect on (correct) judgments under conditions designed to minimize "anxiety;" and (b) morphine (15 mg i.m.) reduced the disruptive effects on reaction time performance produced by self-inflicted faradic shock penalties for "slow" responses; whereas, pentobarbital (250 mg i.m.) did not. In addition to confirming the hypothesis already mentioned, the remarkable stability of performance under the morphine condition in these experiments, regardless of anticipated or actual consequences, suggested another hypothesis, namely, that the analgesic effect of morphine is but one example of a more general effect of that drug—promotion of "indifference" to stimulus and reinforcement conditions, painful or not, without obligatory impairment of psychomotor functioning. In keeping with this hypothesis, it was found [14] that morphine (15 mg i.m.) reduced, whereas pentobarbital (250 mg i.m.) increased, the "range of change" in mean reaction time consequent on variation of "incentive levels," defined in terms of different schedules of morphine reward for completion of the experiments, compared with performance

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under the same "incentive level" conditions in the drug-free state. Incidentally, these experiments illustrate a point stressed by Wikler [43], namely, that the specific effects of a given drug on the central nervous system must be defined in terms of specific *pattern* of effects (e.g., in the case of morphine, "indifference" or perhaps better, "stabilization"), inferred from studies on the effects of that drug (ideally at several dose levels) on a variety of dependent variables under a variety of stimulus and reinforcement conditions.

Other investigators at the Addiction Research Center likewise contributed to understanding the mode of action of morphine under conditions of painful stimulation in man. Using a modified form of the Wolff-Hardy-Goodell radiant heat "pain threshold" method under "normal" and "anxiety-promoting" conditions, Kornetsky [25] found that single doses of morphine reduced significantly the number of "stronger" response judgments and of anticipatory electrodermal responses, and increased motor and electrodermal response latencies measured from the onset of the thermal stimuli, but only under "anxiety-promoting" (so-called "formal") conditions. The effect of morphine on changes in skin conductance during classical conditioning is quite complex. Jones et al. [22] found that during *acquisition* of classically conditioned electrodermal responses (to electric shock stimuli delivered to the calf), morphine 16 mg or pentobarbital 200 mg tended to reduce the degree of conditioning but morphine also attenuated the increase in "tonic" basal conductance relative to placebo during the conditioning period and did so more effectively than pentobarbital. Neither drug impaired the responsivity of the "phasic" electrodermal response. It appeared, therefore, that "tonic" increase in skin conductance, rather than "phasic" electrodermal responses may be correlated with "anticipatory anxiety" during acquisition. On the other hand, comparing unconditioned and tone-conditioned "tonic" and "phasic" responses to intermittent electric shocks delivered to one hand during *retention*, Jones and Ayres [21] found that morphine had no effect on conditioned "tonic" and "phasic" responses but did reduce the unconditioned increase in basal skin conductance that developed during continued testing and that this effect was dose related. The effects of morphine on conditioned responses may therefore differ for acquisition and retention.

In an attempt to develop an animal model of "anxiety associated with anticipation of pain," Hill et al. [10, 11, 12, 18] employed the Estes-Skinner [4] technique, currently referred to as the "conditioned emotional response" (CER). This consists first of training food-deprived rats to press a lever on a variable interval schedule for food-pellet rewards. After the acquired lever-pressing behavior has become stabilized (practically straight line cumulative response curves), a given food-deprived rat is placed in the operant chamber and allowed to press the lever for 4 minutes; thereupon a tone is sounded for 4 minutes, whereupon the tone is terminated together with delivery of an AC electric shock to the feet, strong enough to evoke a visible motor response (NOTE: termination of the tone and shocking is carried out only when the rat is seen *not* to be touching the lever); lever-pressing responses are then recorded for 4 minutes, after which the rat is removed from the operant chamber. A few repetitions of this procedure result in conditioned suppression of lever-pressing for the duration of the tone, followed by transient "rebound" increase in lever-pressing rate immediately after termination of the tone-shock. The ratio of tone-rate to pre-tone-rate, expressed as a percentage, is taken as a measure of the CER. In addition, visual observation of the degree of "freezing" during the tone furnishes a qualitative estimate of the strength of the CER. Drug testing begins with a study of the effects of graded doses of a given drug on lever-pressing rate per se (conditioned operant) over time. Testing the effects of a given drug on the CER (three 4-minute periods described above) is begun (in separate sessions) at a time after subcutaneous injection of the drug corresponding to its peak action on the conditioned operant (determined for each dose of the drug). Morphine, methadone, and meperidine (meperidine tested as an "unknown" drug) slowed lever-pressing rates in the conditioned operant tests and reduced suppression of lever-pressing during the tone period, in a dose-related manner within the analgesic range, and calculation of the relative potencies of these three drugs from the slopes of the dose-response curves yielded values that were very similar to their relative analgesic potencies in this species. Furthermore, it was shown that the reduction of the CER by these drugs was not due to increase in hunger drive, sedation effects per se, motor impairment, auditory impairment, or learning that tone-shock pairing was not aversive under opioids. In these studies, a 50–60 cps tone with higher frequency harmonics of low intensity was employed. Using this tone, it was found that the following drugs produced no significant dose-related effects on the CER: amphetamine, 1.0 and 3.0 mg/kg; pentobarbital, 4.0, 6.0 and 10.0 mg/kg; and chlorpromazine, 1.0, 2.0 and 3.0 mg/kg. Surprisingly, however, LSD–25 in doses of 0.1 and 0.4 mg/kg did reduce the CER in a dose-related manner. However, on testing with a 523 cps tone (which produced a more intense CER, lever-pressing rates during the tone period practically zero), only morphine (3.0, 5.0 and 7.0 mg/kg) reduced the CER in a dose-related manner (other opioids were not tested). It is interesting to note that LSD–25 has been reported [23] to exert "analgesic" effects in some patients with terminal cancer. Also, the failure of nalorphine to reduce the CER suggests that its analgesic mechanism of action differs from that of morphine (e.g., different receptor site of agonistic action).

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While these studies were in progress, clinicians generally thought that reserpine reduced "anxiety." However, Yamahiro, Bell, and Hill [55] demonstrated that the effects of chronically administered reserpine on the CER did not differ from those of placebo injections.

II. Neurophysiological Basis of the Morphine Abstinence Syndrome

1. Chronic decorticated dogs [40, 41]

Cerebral decortication was accomplished in 13 dogs in two operations, a month or more apart, involving craniotomy and removal of all accessible neocortex by suction as well as transection of the olfactory tracts about 5 mm anterior to the optic chiasm. Drug studies were attended with many difficulties and 11 of these decorticated dogs died at various stages of the morphine addiction cycle. After death, gross examination of the remaining brains of these 11 animals revealed that deneocortication was complete in 5; whereas, small bits of occipital or temporal cortex were preserved in 6. However, two deneocorticated dogs survived 12 and 19 months respectively and after completion of all experimental studies, both gross and microscopic examination of the remaining brains showed that all neocortex as well as portions of the basal ganglia and the meso- and archi-cortex of the anterior temporal lobe had been removed. The most extensive studies on conditioning and on cycles of addiction to morphine and methadone were carried out on these two deneocorticated dogs (one male and one female), and the observations may be summarized as follows.

In these preparations, tactile placing reactions were absent and hopping reactions were impaired or abolished. When scratched on the back, they exhibited vigorous licking and chewing movements. In response to sudden noises, they exhibited an orienting response consisting of widening of the palpebral fissures and wagging the head from side to side; or, if the sudden noise was high-pitched, they sprang to their feet. Sudden tactile stimuli (e.g., grasping the back), noxious stimuli (e.g., pinching a toe), or restraint evoked the classical picture of "sham rage." When placed in a corner, they pushed forward obstinately, eroding the skin of the snout. After many months, the deneocorticated dogs ceased pushing obstinately and backed up on contacting the corner. The male deneocorticated dog always squatted to urinate. When an intact female dog in heat was placed in its cage, the male deneocorticated dog showed no reaction. The two deneocorticated dogs would swallow food placed in the oropharynx and ate if the snout was thrust into a food bowl; but they ignored food placed laterally in the bowl. Because several deneocorticated dogs had been lost by aspiration of liquid vomitus, fluid balance was maintained in these two deneocorticated dogs by daily subcutaneous injection of 300–400 ml. of normal saline. These clyses always evoked furious excitement. However, no anticipatory (conditioned) responses were evoked by the preparations for the clyses. One of the deneocorticated dogs had a surgically prepared parotid fistula, and salivated through it whenever he was picked up if he had not been fed that day; this response could not be extinguished by repeated handling not followed by feeding.

Formal attempts to produce classically conditioned morphine salivation were unsuccessful. Subcutaneous injections of morphine, 5 mg/kg, were given once daily in the morning after the animal was placed in a harness in a quiet room for 15 minutes. Occasionally, a subcutaneous injection of saline was substituted for morphine. In an intact normal control dog, definite evidence of conditioned salivation appeared on the third day and rapidly became profuse. In one of the deneocorticated dogs, salivation appeared neither before nor after morphine during a 1-month period. In the other deneocorticated dog, salivation did follow morphine injection, but there was no salivation before, or following a saline injection during a period of 41 days, except when preinjection irritability was very marked. Formal attempts were also made to produce classical time conditioning by regular excitation of the deneocorticated dogs for 20 minutes every 6 hours during a 3-month period with a wire brush charged with faradic current. A general increase in motor activity developed but this bore no relationship to the hours of the day when the unconditioned electrical stimulus was presented. Likewise, formal attempts were made to produce classical conditioning of a discrete motor response to auditory, visual, and tactile stimuli. The unconditioned stimulus was faradic shock applied to one hindleg and the unconditioned response was flexion of the leg, mild escape movements, and barking. The auditory (conditioned) stimulus was a pure tone of 500 Hz presented for 5–6 times followed immediately by the unconditioned stimulus, or for 10 s overlapping the unconditioned stimulus during the last second. The tone always evoked an orienting response but no conditioned responses were observed even after about 1,000 pairings. In one of the deneocorticated dogs, an attempt was made to produce a conditioned avoidance response, The conditioned stimulus was a 500 Hz tone presented for 10 s during the last 5 s of which a grid under the left hindleg was charged with faradic current (accompanied by the buzzer sound from the inductorium); the animal could avoid the shock by raising its leg. However, after 216 trials, no conditioned avoidance responses were observed. In the other deneocorticated preparation, classical visual-motor conditioning was attempted. The conditioned stimulus was an electric light turned on for 5 s followed immediately by

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faradic shock to the hindleg. After 980 pairings over 3 days, no conditioned response was observed. However, a classically conditioned tactile motor was produced in both deneocorticated dogs after several hundred pairings of conditioned and unconditioned stimuli. The procedure consisted of applying 10 successive light strokes to the lower back with a plastic comb (conditioned stimulus) followed immediately by faradic shock to a hindleg. After 604 trials in one and 471 trials in the other deneocorticated dog, discrete conditioned flexion responses appeared in response to the 8th to 10th stroke of the comb, and these remained stable over a period of several days. By omission of the faradic shock, the conditioned responses rapidly extinguished and after a few reinforcements, reappeared. These general behavioral observations and the results of the formal conditioning studies indicate that contrary to Pavlov (loc. cit.), conditioning is not "impossible" in the absence of the cerebral cortex, but nevertheless, conditioning (and hence, the "psyche") is indeed severely impaired. Hence, one would expect that if the opioid-withdrawal syndrome is partly "psychogenic" in animals, then its intensity should be greatly reduced, compared with the intact animal. This expectation was not borne out in the studies on cycles of morphine and methadone addiction in deneocorticated dogs.

In these preparations, single doses of morphine, 2–10 mg/kg s.c., were followed within 3–5 min by salivation and emesis attended by restlessness for 5–10 min after which spontaneous activity was profoundly depressed. "Sham rage" in response to all stimuli was reduced or abolished. The preparations often exhibited extensor rigidity of the forelegs. The orienting and startle responses remained or were exaggerated after small doses of morphine but were abolished by doses over 10 mg/kg. The tooth-pain reaction threshold was elevated, rectal temperature was lowered, pulse rate was slowed, and respirations were variably affected by morphine. Similar effects were observed after 2–5 mg/kg of methadone. During experimental addiction to morphine or methadone over periods of 2–3 months, tolerance developed in varying degrees to these effects, even after increase in dosage up to 25 mg/kg of morphine or 5 mg/kg of methadone every 6 hours. This was especially marked for the depressant effects of these drugs on "sham rage" and tooth-pain threshold. Indeed, the deneocorticated dogs became increasingly irritable as addiction progressed and measurements of tooth-pain threshold had to be abandoned during the latter part of the addiction period because of the preparations' ferocity. For the first 40 days, morphine, 5 mg/kg s.c., was given once daily; during this period, there was little evidence of tolerance to the lowering effect of morphine on rectal temperature and slowing of pulse rate and the initial values of the latter tended to be higher than control. However, when morphine, 5 mg/kg s.c., was given every 6 hours, tolerance did develop to the hypothermic effects; initial values of pulse rate remained depressed. Tolerance to the depressant effects of methadone, 5 mg/kg every 6 hours, on rectal temperature and pulse rate was not apparent.

Continuous records of spontaneous motor activity were obtained by use of a circular pen mounted on a low fulcrum. In this pen, the deneocorticated dog sat, slept or "circled" in one direction only, barely avoiding contact with the linoleum-lined wall of the pen. The tilts of the pen when "circling" were recorded continuously by connecting one edge of the floor of the pen with a sylphon and a closed pneumographic ink-writing device. Control records indicated that the deneocorticated dogs "circled" periodically during the 24 hours of each day in an irregular manner. Single doses of morphine or methadone greatly prolonged the intervals between "circling" activity. When morphine to levels of 5 mg/kg q 6 h over periods of 76–77 days or to 25 mg/kg q 6 h over 55 days, or methadone to levels of 2 mg/kg q 6 h over 35 days or to 5 mg/kg q 6 h over 64 days was administered subcutaneously, "circling" activity per day increased and assumed a regular pattern, increasing an hour or two before each dose of opioid and subsiding within an hour after it was given. Concomitantly with the predrug "circling," the deneocorticated dogs exhibited a marked increase in "sham rage." When morphine or methadone was abruptly discontinued, "circling" and furious "sham rage" persisted continuously for up to 48 hours, and was accompanied by yawning, rhinorrhea, salivation, panting and vomiting. This was followed by persistent rooting and gnawing on the floor of the cage ("circling" and "sham rage" decreased) and by tachypnea, tachycardia, fever and prostration. In one of the animals (during abrupt withdrawal from methadone) a single dose of methadone, 5 mg/kg s.c., suppressed these alarming withdrawal phenomena, the dog sat up and exhibited "sham rage" on handling. The other animal was not treated after abrupt withdrawal of morphine; its pulse rate reached 176/min, rectal temperature 40° C., and after forced feeding, it vomited and died immediately thereafter.

2. Chronic spinal dogs [44, 45]

The investigations on chronic deneocorticated dogs just described indicate that the cerebral cortex is not necessary for the development of tolerance to and physical dependence on morphine or methadone. They also indicate that "psychogenesis" plays a minor role, if any, in the development of these processes. However, inasmuch as the deneocorticated dogs were capable of developing classically conditioned tactile-motor conditioned reflexes, the possibility of "psychogenesis" could not be eliminated entirely. Both for the purposes of analyzing further the neurophysiological mechanisms involved and for eliminating

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"psychogenesis" entirely, studies on tolerance and physical dependence were carried out on chronic spinal dogs. These preparations were made by surgical resection of a segment of the spinal cord in the lower thoracic region (between D–10 and D–12). Careful postoperative attention was required for about a month before the bladder became fully automatic and hindlimb reflexes stable. In the early studies, skin lesions proved troublesome but this was solved by keeping the animals on a bed of wood shavings which absorbed urine and was changed frequently. Details of the methods of eliciting and recording the hindlimb reflexes (isotonically) are described by Wikler and Frank [45]. In these preparations, single doses of morphine (5–10 mg/kg s.c.) or methadone (1–2 mg/kg s.c.) depressed markedly the ipsilateral flexor and crossed extensor reflexes, enhanced the ipsilateral extensor thrust, and had small but variable effects on the knee jerk. After very large single doses of morphine (100–150 mg/kg s.c.) or methadone (40–50 mg/kg s.c.), tonic and clonic convulsions appeared above the level of spinal cord section but not below it. With morphine, addiction periods varied from 29–103 days, the daily dose being increased gradually to 25 mg/kg s.c. every 6 hours. With methadone, addiction periods varied 47–63 days, the daily dose level being increased gradually up to 5 mg/kg every 6 hours. During the addiction periods, marked tolerance developed to the depressant actions of these drugs on the ipsilateral flexor and crossed extensor reflexes but not, apparently, to the enhancing action of morphine on the ipsilateral extensor thrust (however, Martin and Eades [29] found that tolerance also developed to this effect). As addiction continued, the preinjection values of the ipsilateral flexor and crossed extensor reflexes increased both in amplitude and duration.

After abrupt withdrawal of morphine or methadone, the ipsilateral flexor and crossed extensor reflexes continued to increase in magnitude while the ipsilateral extensor thrust and the knee jerk decreased markedly. Spontaneous, rhythmic, alternating flexion and extension of the hindlimbs ("running" movements) appeared as early as 30½ hours after withdrawal of morphine and 9 hours after withdrawal of methadone (dogs in lateral recumbent position, in which the stepping reflex was normally absent). These "running" movements increased in magnitude and frequency until a peak was reached about the 72d–90th hour after morphine withdrawal and the 24th–30th hour after methadone withdrawal, following which there was a gradual return to the preaddiction status of the reflexes over a period of 10–14 days. However, hyperactivity of the ipsilateral flexor reflex persisted for as long as 4 months after drug withdrawal.

Concomitantly with these abstinence changes in the hindlimb reflexes, the dogs exhibited restlessness, tremors, fever, yawning, lacrimation, rhinorrhea, vomiting, and occasionally diarrhea—signs attributable to structures innervated from segments of the neuraxis above the level of spinal cord transection—but these subsided much more rapidly than the hindlimb reflex changes. It should be noted that in these "low" chronic spinal dogs, afferent feedback into the spinal cord below the level of transection could originate in viscera innervated from the neuraxis above the level of spinal cord section. However, much the same hindlimb reflex changes during morphine abstinence were observed by Martin and Eades [29] in studies on acutely and chronically physically dependent "high" chronic spinal dogs, with transection of the spinal cord at C–5 and C–6 segments, above the sympathetic outflow from the spinal cord.

In another study on chronic spinal dogs with transections of the spinal cord at C7–C8, Wikler and Carter [44] were able to precipitate hyperactivity of the ipsilateral flexor reflex and "running" movements with single doses of the opioid antagonist, nalorphine (22.7–30 mg/kg s.c.) 1 hour after a single dose of morphine (10–100 mg/kg) in some preparations, and with smaller single doses of nalorphine (15 mg/kg s.c.) after 2–3 days of administration of morphine, 0.5 mg/kg s.c., every 6 hours, before any evidence of tolerance to the depressant effects of this small dose of morphine was manifest.

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3. Chronic "spinal" man [54]

The admission of a heroin addict with paraplegia due to old luetic meningomyelitis provided an opportunity to investigate, with the patient's informed consent, changes in the lower limb reflexes during cycles of addiction to morphine and methadone for comparison with those in the chronic spinal dog. The patient was paralyzed from the waist down except for feeble flexion and extension movements of the lateral two toes of the left foot. There was complete loss of sensibility to vibration and position sense up to D–6 on the left and D–8 on the right; pain sensibility was impaired over the left lower extremity and completely absent over the right lower extremity and over the trunk up to D–2 on the left and D–3 on the right; touch sensibility was impaired over the right lower extremity and completely absent over the left lower extremity and on the trunk up to D–6 on the left and D–8 on the right. Techniques were developed for eliciting lower-limb reflexes analogous to those in the hindlimb of chronic spinal dogs: nociceptive flexor reflexes, elicited from the skin of the medial aspect of the thigh or leg; and various stretch reflexes (knee jerk static quadriceps, extensor thrust). Single doses of morphine (15 mg) depressed the nociceptive flexor reflex and enhanced all the stretch reflexes. During experimental addiction (to 60 mg of morphine four times daily), tolerance developed to the depressive effects of morphine on the nociceptive flexor reflex but not to the enhancement of the stretch reflexes. On abrupt withdrawal of morphine for 36 hours, the nociceptive flexor reflex became hyperactive and repetitive while the stretch reflexes became hypoactive. Also, spontaneous adductor spasms and mass reflexes appeared. Resumption of the morphine dose schedule abolished these withdrawal signs and restored the state of tolerance already described. On the 57th day of morphine addiction, subcutaneous injection of 6 mg of nalorphine precipitated a violent lowerlimb abstinence syndrome with very marked hyperactivity of the nociceptive flexor reflex, marked hypoactivity of the stretch reflexes, almost constant spontaneous movements and intermittent "galloping" of the lower limbs. Concomitantly with these lowerlimb abstinence phenomena, the patient exhibited "rostral" signs of morphine abstinence: yawning, lacrimation, rhinorrhea, pupillary dilatation, sweating, piloerection, and complaints of generalized aching and abdominal distress. About 1½ hours after nalorphine administration, regular injections of morphine were resumed and the changes noted began to subside within a few hours. Methadone, in a ratio of 1 mg for 3 mg of morphine, was then substituted for 9 days, and then was reduced rapidly over a period of 6 days. Mild "rostral" and lowerlimb abstinence phenomena were noted but the latter did not subside to asymptotic values until about 90 days following withdrawal of methadone.

These studies on the chronic spinal dog and on chronic "spinal" man demonstrate that the spinal cord is one of the sites of morphine action and that the spinal cord is capable of developing marked *chronic* tolerance to and marked *chronic* physical dependence on morphine. Martin and Eades [29] showed that the spinal cord is less capable of developing *acute* tolerance to and *acute* physical dependence on morphine, although "rostral" signs of *acute* tolerance and physical dependence develop readily. Obviously, the mechanisms of acute and chronic tolerance and physical dependence differ. Martin [28] has offered a homeostatic theory of *acute* tolerance and physical dependence which holds that consequent to the effects of morphine on "homeostats" (lowering or raising their "set points") and the abnormal conditions created thereby (hypothermia, hypercapnia), homeostatic regulatory systems respond to bring the internal milieu toward a less abnormal state (acute tolerance). If, after the new state of homeostatic equilibrium is established, morphine is abruptly withdrawn, or a narcotic antagonist is administered, the "set points" of the homeostats are restored to normal and the homeostatic regulatory systems respond vigorously to the still-persisting abnormal internal environment (acute withdrawal syndrome), until this is dissipated. The spinal cord lacks such homeostats and homeostatic regulatory systems. To explain *chronic* tolerance and physical dependence, Martin [28] has proposed a theory of "pharmacological redundancy," according to which normally redundant, morphine-insensitive neural circuits undergo hypertrophy during chronic morphine administration and maintain the function originally depressed by morphine (chronic tolerance). If now morphine is withdrawn abruptly, or a narcotic antagonist is administered, the function is maintained not only by the circuit previously blocked by morphine, but also by the hypertrophied redundant circuits (chronic withdrawal syndrome), until the hypertrophied circuits become redundant again.

Whether or not spinal reflexes can be classically conditioned was investigated by Lloyd et al. [27]. These investigators paired a stimulus (pressure on the tail) which never evoked flexion of a leg, with an electric shock stimulus to the toes of a leg in two "low" chronic spinal dogs. After more than 1,000 pairings, no evidence of conditioned leg flexion was obtained. It can be said, therefore, that insofar as the ipsilateral flexor reflex is concerned, the spinal cord has no "psyche." From these studies it would appear that whether or not morphine abstinence phenomena can, under certain conditions, become classically conditioned (see below), they are unconditioned consequences of repeated administrations of morphine. In man, however, another feature of opioid dependence is persistent opioid-seeking behavior, which can be understood as the consequence of operant conditioning—i.e., reinforcement of self-administration of opioids through their "rewarding" effects in the presence of certain discriminative stimuli (which can also act as secondary, or conditioned reinforcers). Inasmuch as it had been reported by others that both morphine abstinence phenomena and opioid-seeking behavior were abolished or attenuated by bilateral frontal lobotomy [26,33] or by bilateral rostral cingulumotomy [5, 6, 7], investigations were carried out on the effects of such neurosurgical procedures upon these phenomena.

4. Bilateral frontal lobotomy

Wikler et al. [52] compared the intensities of morphine abstinence syndromes evoked by abrupt withdrawals before surgery, during the immediate postoperative (1–2 days) period, and 9–46 days after bilateral frontal lobotomy in three chronic schizophrenic patients and by test withdrawals 18 days after unilateral and again 10 days after completion of bilateral frontal lobotomy in one nonpsychotic addict with chronic intractable phantom limb pain, all of whom had been stabilized on known daily doses of morphine prior to and between the test withdrawals. In all cases, bilateral frontal lobotomy was deemed indicated for therapeutic purposes by an independent medical-psychiatric board. At no time during the study did any of the three psychotic subjects display opioid-seeking behavior; hence, only physiological abstinence

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phenomena could be examined in these individuals. Prior to surgery, all three psychotic subjects displayed mild to severe physiological abstinence changes during test withdrawals. When tested again immediately after recovery from surgical anesthesia, these were obtunded; however, when retested again after recovery from postoperative lethargy and general unresponsiveness (during which time morphine injections had been resumed), all three subjects exhibited physiological abstinence phenomena comparable in pattern and intensity with those observed prior to bilateral frontal lobotomy. In the case of the single nonpsychotic patient, the test withdrawal after unilateral frontal lobotomy evoked not only yawning, lacrimation, mydriasis, sweating, piloerection, emesis, etc., but also opioid-seeking behavior—complaints of distress (although the phantom limb pain was partially relieved), demands for drugs, and threats of suicide. However, after completion of bilateral frontal lobotomy, test withdrawal evoked all of the physiological abstinence phenomena and if asked, the patient admitted that he was sick, but he made no complaints and did not demand narcotics. It was concluded that the integrity of the frontothalamic connections is essential for the mechanisms involved in opioid-seeking behavior but not for physiological morphine abstinence phenomena. The transient attenuation of the latter in the immediate postoperative period was attributed to cerebral shock or diaschisis.

5. Bilateral cingulumotomy and other limbic system lesions

These investigations were carried out in rats. Martin et al. [32] had demonstrated that in this species, large doses of morphine (e.g., 100 mg/kg) produce, in the nontolerant animal, marked depressant effects on general motor activity, and slight depression of body temperature and metabolic rate. In rats made tolerant to 80 mg/kg/day or 320 mg/kg/day, comparable single doses of morphine (100 or 140 mg/kg) produced a marked increase in motor activity and marked elevation of body temperature and metabolic rate. Upon abrupt withdrawal of morphine, abstinence phenomena proceeded in two phases: (a) The early abstinence syndrome, peaking at about 24 hours after withdrawal of morphine: precipitous fall in body temperature to levels below that of normal control rats; marked increase in frequency of "wet dog" shakes (spontaneous twitches of the skin over the back resembling those of a dog shaking water off its back); marked increase in head shakes; decrease in water drinking to levels below those of normal control rats; fall in metabolic rate; a change in pattern of motor activity (a tendency to sleep in the sitting posture with more preening and scratching and less standing, walking, exploring, and gnawing); increased urination and defecation; hostility; and more slowly (maximal on second or third day), fall in body weight. (b) The protracted abstinence syndrome: about 72 hours after abrupt withdrawal of morphine, when the early abstinence syndrome had largely subsided, the abstinent rats began to gain weight rapidly, water drinking increased to about 30 percent above that of control animals, body temperature and metabolic rate rose slightly, while the frequency of "wet dog" shakes remained slightly elevated. These changes persisted for up to 6 months, when the study was terminated.

In addition, Wikler et al. [47] had shown that whereas non-water-deprived normal rats will drink equal volumes of water or a 5 μg/ml concentration of etonitazene (an opioid which is 1,000 times as potent as morphine for analgesia in the rat) in a single tube, no-choice situation, morphine-addicted rats in early abstinence will drink far larger volumes of the 5 μg/ml (or 10 μg/ml) concentration of etonitazene, which suppresses the early morphine-abstinence syndrome. Also, Wikler and Pescor [50, 51] had reported that formerly morphine-addicted rats will continue to drink significantly more etonitazene solution (5 μg/ml) than normal control rats whereas drinking of water is nonsignificantly different in two-tube choice tests conducted at intervals of a week or more and continued for various periods, up to one year ("relapse" tests).

Accordingly, Wikler et al. [49] investigated the effects of bilateral lesions in the cingulum bundle, the dorsomedial thalamic nucleus, the septum, or the anterior temporal lobe (amygdaloid complex and ventral hippocampus) on early morphine-abstinence phenomena (decreased water intake, increased no-choice intake of etonitazene, 5 μg/ml; increased "wet dog" frequency, fall in body temperature); the protracted morphine abstinence syndrome (increased 24-hour water intake); and on "relapse" tendencies (significantly increased intake of etonitazene, 5 μg/ml, with no significant differences in water intake) in choice trials at intervals between 9–72 days after abrupt withdrawal of morphine. None of these bilateral limbic system lesions had any significant effect on the early morphine-abstinence syndrome, the protracted morphine-abstinence syndrome or "relapse" tendencies, except that the cingulum bundle lesions did attenuate the protracted abstinence syndrome (as measured by 24-hour water consumption). Nor did any of these limbic system lesions affect the suppressive effects of no-choice etonitazene drinking or of intraperitoneal injections of morphine upon the early morphine-abstinence syndrome.

III. Conditionability of the Morphine-Abstinence Syndrome and Relapse

Despite the evidence presented above that the physiological signs of

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morphine-abstinence can be demonstrated in nonconditionable animal preparations, the possibility remained that in the intact animal or man, given appropriate contingencies of reinforcement and conditioning, morphine-abstinence phenomena and opioid-seeking behavior could become conditioned and thereby play a powerful role in relapse. The first hints that such a process occurs in human addicts·were obtained by Wikler [42] in a long-term (over 4 months) psychodynamic study of a postaddict during self-regulated readdiction to morphine. Under the terms of the experiment, the subject was permitted to ask for and receive by any route (administered by an aide or by himself) any drug in any amount (up to a "ceiling" judged safe by the experimenter) at any time of day or night for an unspecified period of time which, however, would not be less than 1 month; also, the subject would be informed 1 month in advance of the termination date of this agreement. It was stressed that the experimenter had no interest in the subject's getting himself "hooked," but if he should, the experimenter would advise on how the subject might withdraw himself from whatever drug he was taking. The subject assured the experimenter that he would not get "hooked," and elected to take 30 mg of morphine i.v. as his first dose. Two hours later he took another 30 mg dose of morphine i.v., and over the next 3½ months he took morphine i.v. exclusively every day, gradually increasing the frequency and dose in stepwise fashion, attaining an overage level of about 1,100 mg/day in 12 divided doses just before the "one month's notice" date. After about 2 weeks of this final period, he asked for and was given advice on the methadone substitution and withdrawal method, which he adopted initially; however, 3 days before the termination date of study, he reverted to morphine i.v., taking 1,000 mg of morphine (plus 30 mg of methadone) in divided doses during the last day, following which a rather severe but typical morphine-abstinence syndrome ensued.

From the patient's "free associations," manifest dream content, and observation of his behavior during this study, a number of conclusions were drawn: (a) the "euphoric" effects of morphine (verbally in keeping with the MBG scale items, though the "energized" subject spent most of the time in bed "nodding" and "coasting") disappeared within a few days (except for the momentary "thrill" of morphine i.v.) and was replaced by a prevailing dysphoric mood which continued throughout the remainder of the study; (b) the major motivational variable for continuation of self-injection of morphine was not fear of the withdrawal syndrome (the patient denied such fear and in fact, "elected" to withdraw himself abruptly at the end of the termination date) but rather the gratification achieved through the suppression by each dose of morphine, of the mild abstinence changes (perceived by the subject as a "need" or "craving") that ensued a few hours after self-administration of the past previous dose—as the subject put it, "A steak tastes good anytime, but if you are a little hungry, it tastes even better;" and (c) with the development of physical dependence, all other variables become subsidiary (and often conflictful) to (b) above. Also, strongly suggested by the subject's "recollections," were that "hustling" (operant behavior directed toward obtaining opioids) is reinforcing in its own right—i.e., brings about reinforcements in addition to the acquisition of drugs; and that episodes of relapse in the past, attributed by the subject to unexplained "illnesses" or feelings of "disgust" at times of chance encounters with other addicts may, in fact, have been due to evocation by the latter of conditioned abstinence phenomena. These conclusions furnished a basis for construction and testing of a "conditioning theory of drug dependence and relapse" in animals.

Anamnestic data obtained in the interviews also yielded information on the effects of opioids on sexual behavior (as perceived by the subject): in the nontolerant state, opioids delay orgasm, thereby prolonging penile erections, though libido may be reduced; as tolerance (and physical dependence) develops, both penile erections and orgasms become increasingly difficult of attainment, while libido is totally absent; during the first few days of the abrupt opioid-abstinence syndrome, nocturnal emissions and increased libido often occur.

Other early studies of behavioral changes in the tolerant and physically dependent state were those of Brown [2] who found that in this state, differences in electrodermal responses to "disturbing" and "nondisturbing" word stimuli were reduced, and that responses on the Rorschach test showed lesser "constriction," compared with responses in the drug-free state.

Brown's findings are difficult to reconcile with the grossly obvious "dysphoric" state of the subject after the first few days of self-regulated readdiction to morphine, and with the elevated scores on the MMPI "hypochondriasis" and the PCAG scales reported by Haertzen and Hooks [8] in subjects tolerant to morphine administered "passively," as well as with the elevated PCAG scores (indicating lethargy, sedation, weakness and decreased motivation), elevated MMPI scores on the "hypochondriasis" and "schizophrenia" scales of the MMPI, and items relating to withdrawal from social interaction on the Chronic Opiate Symptom scale in subjects made tolerant to methadone, reported by Martin et al. [31]. In this last-mentioned study, the effects of chronic administration of methadone on sexual behavior (masturbation) were found to be strikingly similar to those of opium and/or morphine as recalled by the subject described above. During the control period, the mean frequency of masturbation and spontaneous nocturnal emissions was, respectively, 1.5 and 0.2 times a week, while during the ascending dose phase and early stabilization the frequency of masturbation was 0.1

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a week, and there were no reported nocturnal emissions. During the last four weeks of stabilization, sexual activity as measured by the frequency of masturbation and spontaneous nocturnal emissions had returned to almost control levels with a weekly frequency of 1.0 and 0.2, respectively. During this time, patients reported that it was still difficult to obtain an erection and to ejaculate. During the early phase of the abstinence syndrome, patients had many spontaneous emissions, which were for the most part not associated with orgiastic feelings.

Of great interest in connection with the claim that "maintenance" on high doses of methadone (e.g., 100 mg/day) suppresses "drug hunger" and heroin-seeking behavior are the findings of Martin et al. [31] that in the control (drug-free) state, all 12 subjects avidly performed the arduous task of riding a modified exercise bicycle 10 miles in 1 hour or less for a 4 mg hydromorphone (Dilaudid) reward (equivalent to 30 mg of morphine) given intravenously (an operant task devised by B.E. Jones); when daily methadone dose level reached 55–80 mg/day, four of the subjects continued to work for hydromorphone, and two of these continued to do so (though skipping an opportunity occasionally) even when the daily dose level of methadone was 100 mg/day. One possible explanation of these findings is that the continued "hustling" exhibited by 4 of the 12 subjects was due to incomplete cross-tolerance between methadone and hydromorphone; another possibility is that, assuming complete cross-tolerance at least at the 100 mg/day methadone level, "hustling" for hydromorphone was maintained by some secondary (conditioned) reinforcing effects of the latter drug which the subjects could discriminate from those of methadone, and which did not provide primary reinforcement.

The hypothesis that through conditioning, previous physical dependence can become a powerful factor in facilitating subsequent relapse was first proposed by Wikler [39]. In support of this hypothesis were "recollections" elicited from postaddicts during interviews about the precise circumstances of their previous relapses to heroin or other opioids. Invariably, they attributed relapse to the desire to "get off the natural" or "to get high," but closer questioning revealed in many instances, that relapse occurred when the former (cured) addict was en route back to his home environment, or when he unexpectedly encountered an active addict or "pusher" on the street. Under such circumstances, the former addict felt "sick" (chills, running nose, watery eyes, nausea—"like the 'flu,' Doc") and instantly started looking for "a fix." On two separate occasions about a year apart, psychiatrists conducting group therapy sessions for postaddicts at the USPHS hospital in Lexington, Ky., related that when the subject of discussion turned to "dope," the postaddicts began to yawn and to wipe their noses and eyes. It is remarkable that in no instance did the postaddicts recognize this "flulike" syndrome as (conditioned) opioid-abstinence phenomenon. To be sure, they report a "high" (called "euphoria" by the observer) after self-administration of heroin or other opioid under such circumstances, but it may be questioned whether the addict is able to discriminate the "high" produced by the direct from the "high" produced by the indirect primary pharmacological reinforcing actions of the opioid—namely, the suppression of conditioned opioid abstinence.

To test the hypothesis that morphine-abstinence phenomena can be classically conditioned and together with operant conditioning of opioid-seeking behavior can dispose to relapse, Wikler [50, 51, 53] carried out a series of investigations on the rat in the laboratories of the Addiction Research Center, although he had retired from the USPHS to join the faculty of the Department of Psychiatry, University of Kentucky Medical Center, Lexington, Ky. In the first of these studies, rats (male, Wistar, about 4 months old) were made tolerant to and physically dependent on morphine by gradual escalation of dose of morphine i.p. to a level of 200 mg/kg daily, given in a single injection at about 7:30 a.m., which was maintained for 4–6 weeks after which injections were terminated abruptly. Concomitantly, rats matched for initial weight received saline injections i.p. on the same schedule. Thus, during the "maintenance" period, the morphine-injected rats (Es) underwent daily cycles of early (nocturnal) morphine abstinence and suppression of such abstinence as well as morphine intoxication the next morning. In the case of the saline-injected rats (Cs), only the normal cyclic events characteristic of this species obtained (daytime quiescence, nocturnal activity, eating, and drinking). In accordance with this experimental design, conditioning procedures, where carried out, were introduced in the late afternoon (about 12 h after the last previous injection) and allowed to operate until the time for the daily injection the next morning. In a first conditioning study, it was shown that provision of temporal contiguity between a discriminable environment ("linear" maze) and the 12–24 h morphine abstinence syndrome on repeated occasions resulted in classical conditioning of "wet dog" shakes to that environment, which persisted up to 155 days after abrupt withdrawal of morphine. Concomitantly, provision was made for operant conditioning of etonitazene drinking behavior by "no-choice" drinking of a 5 μg/ml solution of etonitazene during a number of the 12–24 h nocturnal abstinence periods in half of the Es, with anise flavor added to the etonitazene solution as a cue, while the other half of the Es drank anise-flavored water under the same "no-choice" conditions (two groups of Cs were treated in exactly the same manner). In "relapse" tests conducted at intervals of one or more weeks nocturnally (8:00 p.m. to 8:00 a.m.) beginning 9 days after abrupt termination of injections (morphine in Es; saline in Cs), Es, regardless of whether or not they had been given the

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opportunity (which they utilized) to suppress the 12–24 h morphine-abstinence syndrome by drinking anise-flavored etonitazene, consumed a significantly greater proportion of the fluids offered them in the "choice" drinking "relapse" tests (anise-flavored etonitazene solution vs. plain water) in the form of anise-flavored etonitazene solution than Cs, in tests extending through the 58th day after termination of injections, and again on the 142d day, following successive etonitazene and anise-flavor extinction sessions, and a final reinforcement session. A replication of this study, using tactile-visual cues instead of anise flavor, yielded comparable results, with regard to both classical conditioning of "wet dog" shakes and "relapse" of Es, regardless of whether they had received formal operant training or not. Another striking finding in both the original and the replicate studies, was behavior of Cs vis-à-vis etonitazene drinking. When offered only etonitazene (5 μg/ml) to drink from 8:00 p.m. to 8:00 a.m. for the first time, or only water over this period on another occasion, the ingested volumes of etonitazene solution and of water do not differ significantly. However, on repeated exposure to the etonitazene, Cs developed a progressive aversion to the drug solution in these studies. It appears therefore, that etonitazene, 5 μg/ml, is not reinforcing for normal rats. In an attempt to account for the reinforcing properties of the etonitazene solution for formerly physically dependent rats even without formal operant training, new groups of rats were treated with morphine or saline on the "addiction" schedule described above (final "maintenance" level for Es, 200 mg/kg i.p.) without any operant training whatever, and then injections were terminated abruptly. After the measured signs of early abstinence in Es had subsided, "choice" drinking tests (etonitazene, 5 μg/ml vs. plain water) were made at intervals of one or more weeks, together with two measures of "protracted" abstinence (24-hour tap water intake and "wet dog" shake frequencies, prior to each "choice" test). In these "choice" tests, differential visual-tactile cues were assigned to each rat on the first "choice" trial on the basis of a table of random numbers, and retained for each rat thereafter. In this study, a more stringent criterion of "relapse" was adopted, namely, Es were said to have "relapsed" if the mean volume of etonitazene solution consumed by them in the "choice" tests was significantly greater than that consumed by Cs, provided that the mean volume of plain water consumed by Es was either less, or not significantly different from that consumed by Cs. According to this criterion, Es "relapsed" in tests extending over approximately 1 year. In contrast, the signs of "protracted" abstinence measured (increased 24 h tap water intake; increased "wet dog" shake frequency) were not significant in tests conducted after the 23d day of morphine abstinence.

Considering alternatives other than "protracted" abstinence as an adequate (or sole) explanation of the persistent relapse tendencies of Es, Wikler hypothesized that while Es were "maintained" on morphine, 200 mg/kg each morning, certain of the "interoceptive" actions of morphine acquired secondary (conditioned) reinforcing properties through repeated (daily) temporal contiguity with suppression of the morphine-abstinence phenomena that developed during the night before; such secondary reinforcing properties would be shared by etonitazene (an opioid) which, if ingested in "choice" tests even long after withdrawal of morphine, would reinforce drinking from the etonitazene tube, rather than from the plain water tube. Testing this "interoceptive conditioning" hypothesis with choice-drinking techniques would be very difficult, but one of its postulates, namely, the persistent potency of secondary reinforcers so generated, was investigated by Wikler et al. [53]. Two groups of Es, "maintained" on 200 mg/kg i.p. each morning, had access to single drinking tubes containing anise flavor (a gustatory-olfactory "exteroceptive" cue) plus either etonitazene, 5 μg/ml, (one group) or plain water (the other group) on 9 nights (8:00 p.m. to 8:00 a.m.) over a 25-day period; two saline-injected groups of Cs were treated similarly. After abrupt withdrawal of morphine (or saline), and subsidence of the measured signs of early abstinence in Es, all rats were given nocturnal "choice" drinking tests, anise-flavored *water* vs. plain *water*, at intervals over 287 days. Analysis of variance revealed that through the 137th day after withdrawal of morphine (or saline), Es that had had access to anise-flavored etonitazene solution during previous nocturnal morphine abstinence drank significantly more anise-flavored *water* than any of the other groups, while there were no significant differences among the four groups as regards consumption of plain water. These data indicate that even a pharmacologically inactive cue (anise flavor) can acquire secondary reinforcing properties through temporal contiguity with suppression of morphine abstinence, which persist for months after withdrawal of morphine, independently of any proclivity to "relapse" generated by persistent tolerance to morphine, or by "protracted" abstinence, which could not have played any role in the outcome of these experiments. While not proving the "interoceptive conditioning" hypothesis of relapse, the results of this study are consonant with it.

It may be pointed out here, that this hypothesis has several important implications for human postaddicts with histories of repeated episodes of early morphine abstinence and suppression of abstinence by self-administered opioids, viz.: relapse may be "triggered" by a single dose of an opioid, given or taken for whatever reason; relapse may be "triggered" by the occurrence of "interoceptive" states generated by illness, "anxiety" or other nonpharmacological events, some elements of which are also involved in the opioid-abstinence syndrome; people in control of opioid supplies for "maintenance" programs are likely to acquire powerful secondary reinforcing properties, which may be used

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therapeutically or sociopathologically vis-a-vis the patient; and treatment programs aimed at achieving permanent opioid abstention, such as temporary maintenance on narcotic antagonists [30], must include provisions for active extinction of conditioned abstinence, primary and secondary pharmacological reinforcement. Otherwise, relapse may be expected after the narcotic antagonist is discontinued.

Summary

In studies on man, it has been demonstrated that "analgesic" doses of morphine (15 mg s.c. or i.m.) do not impair the ability to discriminate intensities of painful electric shocks to the hand. However, under experimentally induced conditions of "anticipatory anxiety," intensities of such shocks are overestimated and morphine reduces this error. Morphine also reduces the disruption of performance in reaction time studies produced by anticipation of self-inflicted electric shock penalties for "slow" reaction times. This "indifference"-producing action of morphine was likewise demonstrated in a study on variation of reaction times under different incentive schedules, without painful stimuli. In contrast, 250 mg of pentobarbital i.m. had no such effects. It appears, therefore, that in man, morphine analgesia is one consequence of its overall "indifference" or "stabilization"-producing action.

In chronic deneocorticated dogs, chronic spinal dogs, and in a chronic "spinal" man, it was demonstrated that single doses of morphine or methadone exert subcortical actions, that tolerance develops to some of these effects, and that severe morphine or methadone abstinence phenomena ensue when morphine is withdrawn abruptly or when a narcotic antagonist (nalorphine) is administered. In addition, studies on deneocorticated dogs showed that the capacity of these preparations to acquire classically conditioned reflexes was severely impaired and studies on chronic spinal dogs indicated that hindlimb reflexes in these preparations could not be classically conditioned at all. It may therefore be concluded that opioid abstinence phenomena are unconditional, though this does not preclude the possibility that under appropriate stimulus and reinforcement conditions, they may be conditional (see below).

Studies on patients requiring bilateral frontal lobotomy for therapeutic reasons indicated that while this procedure reduces or abolishes opioid-seeking behavior, it has no effect on the physiological signs of morphine abstinence after abrupt withdrawal of the drug. In rats, bilateral lesions of the cingulum bundle, the dorsomedial thalamic nucleus, the septum or the anterior temporal lobe had no effect on the signs of morphine abstinence in this species, or on relapse tendencies.

Anecdotal evidence obtained in interviews with addicts and post-addicts suggests that frequent temporal association between episodes of acute opioid abstinence and specific environmental stimuli (other addicts, "pushers," drug-available neighborhoods) could lead to classical conditioning of the former to the latter, and with operant conditioning of opioid-using behavior (self-administration of opioids) could play an important role in relapse long after "cure" (detoxification). In support of this hypothesis, it was demonstrated that in the rat, a morphine-abstinence sign, the "wet dog" shake, could be classically conditioned to a specific environment and that such conditioning could persist for up to 155 days after withdrawal of morphine. However, previously physically dependent rats "relapsed" to drinking an opioid (etonitazene) in aqueous solution for up to 1 year following abrupt withdrawal of morphine, whether or not formal operant conditioning procedures had been carried out. It was thought that this was due to the special morphine-injection schedule used in making the rats physically dependent, under which "interoceptive" conditioning could have taken place despite the omission of "exteroceptive" operant conditioning procedures. This inference was supported by the results of a study in which a secondary reinforcer (anise flavor) was added to the etonitazene solution which one group of physically dependent rats drank on several occasions while acutely abstinent from morphine, while another group of physically dependent rats drank anise-flavored water under the same conditions; two groups of control (saline-injected) rats were treated likewise. In choice-drinking tests (anise-flavored water vs. plain water) conducted at intervals after abrupt and permanent withdrawal of morphine, the first-mentioned group drank significantly more anise-flavored water than any of the other groups for 137 days after withdrawal of morphine (or saline), while the consumption of plain water was not significantly different among the four groups.

The "conditioning" hypothesis of relapse suggests the importance of experimental extinction of both classically conditioned opioid abstinence and of operantly conditioned opioid-seeking behavior in treatment programs such as temporary maintenance on narcotic antagonists that aim at eventual permanent abstention from opioid use.

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Dr. John A. O'Donnell, *Social Science Section, Addiction Research Center and Clinical Research Center, 1962–74*

Sociological and Epidemiological Studies

John A. O'Donnell, Ph.D.

The Social Science Section had a rather brief history within the Addiction Research Center. Born in June 1962, it transferred over to the Clinical Research Center late in that decade in the days when it was hoped that the activities of the latter would come to match its name. It came to an end when the Clinical Research Center did, in 1974.

But in that brief life the Section achieved some successes, and those who staffed it have continued to contribute to research in the drug field. The usual staffing pattern, with minor fluctuations from time to time, was three professional positions, three or four research assistant and clerical positions, and in the last years, three interviewers. Through the three professional slots passed some six sociologists and four anthropologists. Counting their publications both while in the Section and

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since leaving it, and without being certain that my count is complete, they have authored slightly over 110 journal articles, 36 book chapters, and have authored or edited 15 books. These figures include only those whose subject matter was drugs.

The earliest studies undertaken by the Section were followup studies, specifically mine [11] on Kentucky addicts and Ball's [5] on addicts from Puerto Rico. A major aim of these was methodological, and they established a number of points of importance:

1. It was possible to locate almost all ex-patients, even those who had left the hospital more than 20 years earlier.
2. It was possible to obtain interviews with those who were still alive, with amazingly low refusal rates, and to obtain information on both living and dead subjects from a variety of record sources, and a variety of informants including parents, siblings, spouses, children, physicians, and both addict and nonaddict friends.
3. The acquisition of data from a variety of sources made it possible to check the reliability and validity of the information obtained, as described in Ball's [2] paper on this subject.
4. The studies were the first field studies to collect urine specimens as a check on statements about current drug use, and again the refusal rate was very low—about 3 percent in each study.

Parenthetically, I might note that at the time these studies were done we did not fully appreciate how fortunate we were in using fairly small samples—under 300—nor how important was the quality of the field staff. I learned this only in the past 2 years, by directing a nationwide survey with a sample of 3,000, and an interviewing staff which started at 160 interviewers. The larger the sample, the more interviewers are needed. The average level of the interviewing staff is necessarily lower; I do not expect any of the 160 to become Assistant Surgeon Generals in the Public Health Service, as did 100 percent of the field staff of the Kentucky study—Karst Besteman. Further, as interviewers multiply and their level of competence declines, one cannot use unstructured interviews, but must design fixed schedules, with complex skip patterns, and one result is less data for a given period of interviewing time.

The Kentucky and Puerto Rico followups, in contrast, relied on highly motivated field staff, with long experience in clinical interviewing. They did not need detailed instructions; their understanding of the purposes of the studies could guide their conduct of the interviews. Indeed, I find it difficult to imagine how the survey approach could be used with informants other than the research subjects, for the purpose of verifying statements about drug use, since the content of interviews with informants depends so much on what has emerged in the interview with the subject.

Some of the substantive findings of these followups also were important. Most earlier studies had covered relatively short periods of posttreatment time, and emphasized the high proportion of relapses. These studies too, found most subjects to have relapsed, but also found that most had had periods of abstinence, with indications that the periods of abstinence tended to become more frequent and longer as the years passed. These findings have since been supported by Vaillant's studies [15].

The followup studies also provided data which clarified the relationship between addiction and other variables. One of the best examples may be the relationship between addiction and crime, long known in broad outline, but seen in greater detail when longitudinal data were available.

The Kentucky sample included subjects whose addictions began over a 60-year range, so it was able to demonstrate how, over the decades, addicts increasingly came from men who had criminal records prior to their use of narcotics. Both the Kentucky and Puerto Rico studies documented the increase in crime following the onset of addiction, and in the Puerto Rico study Ball was able to demonstrate that this was specifically true of the years during which his men were addicted, while their rate of arrests was only one-fifth as high in the smaller number of years in which they were abstinent. Ball was also able to demonstrate a much lower rate of arrests and time in prison for those whom he classified as cured, on the basis of 3 consecutive years of abstinence, despite the fact that in earlier years their arrest rate was essentially the same as those not cured, with whom they were compared.

The findings of the studies also permitted at least partial checks on the adequacy of some of the social science theories advanced to explain addiction. They clearly supported the importance of subcultural ties in the transmission and maintenance of addiction, and were clearly inconsistent with the anomie or blocked opportunities explanations. There was little support for Winick's hypothesis of maturing out of addiction, and even that little may mean only that when you stop doing anything, you are older than when you were still doing it.

Another early interest of the Section was epidemiological research. John Ball was responsible for a most valuable tool, the building of an IBM card file on all admissions to the Lexington and Fort Worth Hospitals from their opening days. While the number of variables available for punching was small, the imagination of several investigators made them produce a surprising variety of studies.

Today there are literally thousands of treatment agencies for drug users, and it is easy to forget how few there were up to about 10 years ago. Indeed, for a period of about 30 years, the two Public Health Service hospitals were the major, and for much of that time almost the only, treatment centers for narcotic addicts. No one ever believed that admissions to the two institutions were a representative sample of all addicts in the United States, but they came closer to being such a sample than any other available source of data. With caution, then, data on hospital admissions could be used to trace historical changes, as Ball [4] did, for example, with respect to the changes in geographical distribution of addicts, and distributions by age and race, or as I did [12] with respect to the spread of the use of the intravenous injection of narcotics.

These data on admissions were the sole base for some studies, like Bates' [7] paper on "Narcotics, Negroes and the South." Within a short time after the Section began work, they were supplemented by more detailed recording of data on new admissions and discharges from both hospitals. Such data were used by Ball [1], for example, in his well-known paper "Two Patterns of Narcotic Drug Addiction in the United States."

This paper was one in a long tradition of defining of types of addicts, and was followed by others tracing out the characteristics of specific groups. The groups were sometimes defined racially, as in Ball's work on Puerto Ricans and Chinese, and the work of Bates [7] and Chambers [10] on Negroes and Mexican-Americans. Sometimes the group was defined by the clustering of characteristics, as in the papers by Stephens and Slatin [14] on the street addict, or of Campbell and Freeland [8] on the hippie. A number of papers focused on the similarities and differences between male and female addicts.

The early epidemiological studies were based on admission records of the two hospitals, and later on expanded records at the admission and discharge, collected by Medical Records personnel. This, of course, was too limited a data source as research questions became more precise and more complex, and when resources became available the Section began to collect its own data on newly admitted patients. One method was a formal, structured interview conducted by three interviewers employed and trained for that specific function. The first project collected voluminous data on the first 1,100 NARA patients admitted to the Lexington Center, and a monograph presenting the major findings is now being prepared for publication. The interview schedule was then revised and shortened, though some new areas of data were added, and this was used for almost 5,600 patients. These data, unfortunately, have never been analyzed, but they are available to investigators in the data bank at Texas Christian University, and I hope will soon be exploited.

The professional staff of the Section also conducted interviews, sometimes structured and more often not, as specific questions arose. The card files which have been mentioned were invaluable for identifying the samples wanted. I remember working on the question of when and how the intravenous route became common among narcotic addicts.

From the admission records it was easy to identify samples of admissions at 5-year intervals, beginning in 1935, and then to abstract desired information from the hospital records of patients. From that analysis, and from a literature search, it seemed fairly certain that intravenous use began in the United States not long before 1930, but where and why and how were unclear.

What was obviously needed was some interviews with long-time addicts, so one day in late 1966 I told Mrs. Cottrell—who deserves as much credit for the accomplishments of the Section as any social scientist who ever worked in it—that I wanted to see some patients whose drug use had begun before 1930. She ran the cards of in-house patients through the sorter, and I had five interviews the next day.

Weppner and Stephens [18] used the same technique to locate the subjects they needed—those who had been in methadone maintenance programs—when they were interested in the study of cheating by patients in such programs. This was also the way to locate a sample if you wished, as Ball [6] did, to look at primary methadone addiction or, as Weppner [16] did, at those who began narcotics use with codeine.

This interest in specific drugs, and the characteristics of those who used them, continued. Other drugs that became subjects of publications were pentazocine, propoxyphene, cocaine, oxymorphone, and methaqualone, as well as drug classes like sedatives and amphetamines.

Among the more important of these studies, important because of the claims of many social scientists that marihuana use did not in any sense lead to heroin use or to the use of other drugs, was a series of studies examining the relationship between use of marihuana and other drugs [3, 9, 17].

There was an inherent limitation on such studies, based on samples of hospitalized narcotic addicts. If you imagine the simplest possible table to examine the relationship between marihuana use and use of narcotics, a two-by-two table formed by dichotomizing on the two drug classes, two cells are vacant because all in the sample have used narcotics. So these had to be filled in by data from other studies, often less detailed then one would want. What is really needed to settle the question is data on drug use in the general population. In a current study, in which the field work ended only a few weeks ago, we have such data, and expect to show within a few months that marihuana use is almost a necessary, though far from a sufficient, condition for other illicit drug use [13].

Let me now move away from the specifics of what the Social Science Section did, and speak a little about what the National Institute for Drug Abuse can learn from its brief history.

Up until very recently, it was rare for social scientists to make a career or even spend an appreciable part of a career, in research in the area of drug use. The usual pattern was that one year an investigator would be doing a study on the family, the next year on drugs, and the year after on crime, or the problems of developing countries in Africa.

One of the major values of the Section was that it afforded a few scientists the chance to maintain a focus on one small area for years. Administrative advantages were obvious: the development of a core of highly skilled research assistants and the building up of data files. Professionals had the opportunity to develop expertise, for example, to become really familiar with the literature. Studies tended to be cumulative, as similar questions were asked about different groups, and as similar findings emerged under differing conditions. Where so little was known, it was desirable to begin with the establishment of facts, guided by the inadequate theoretical formulations that then existed, and still exist. Even the early studies were able to bring into question the adequacy of existing theories, and I like to think that if the Section had lasted longer, at least some of its staff would have been suggesting new theories.

The Section was lucky to be part of the Addiction Research Center and of what was then the National Institute of Mental Health. The administrators and leaders of research were superb, and indeed I came to learn that good research administrators are rarer and more valuable than good researchers. What pressure there was to publish came from within us, or from colleagues in our own disciplines, not from administration. Indeed, we were told not to rush, to check our facts, to take our time.

It was a luxury to have adequate time to analyze data, and rewrite reports as many times as seemed necessary. Research support for specific projects is fine, and has produced many valuable studies. But often this approach means 2 years for planning a study and collecting data, and 2 months for analysis. Even the early stages must be interrupted to prepare grant applications for the next project. There is much to be said for a firm, continuing program which permits a steady progression of work.

Such programs now are established in a few cities and States, and I suggest to NIDA that some appreciable part of the funds available for supporting research should be reserved for the support of programs, as distinguished from the support of projects. I further suggest that there is still room for a social science research program at the Federal level. Whether it should administratively be part of the Addiction Research Center, or of the Research Branch within NIDA, I do not know, and it may not make much difference. Physically, its office could be in Lexington, but most of its activities would be elsewhere.

Even when the Clinical Research Center, and its predecessor, the PHS Hospital, were active, the studies possible for a Social Science Section utilizing their facilities and patients were too limited. Now there would be no rationale at all for restricting studies to persons available in Lexington. The questions that need answers are about the wider world, and need to be studied there. Many would best be studied by a continuing research organization. I would like to end this paper with the strong recommendation that consideration be given to the reestablishment of the Social Science Section.

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DR. JOHN C. BALL, *Chief, Sociology Unit, Addiction Research Center, 1962–68*

An Optimal Environment for Social Science Research Pertaining to Drug Abuse

John C. Ball, Ph.D.

Dr. O'Donnell has most adequately described the accomplishment of the Social Science Section during its 12-year history, 1962–74. I should like to develop further this exposition with particular attention to the advantages of the research environment at the Lexington Hospital.

Lest I be accused of provincialism, institutional bias or flattery, it should be stated at the outset that there is no single research environment which is ideal for pursuing social science research pertaining to drug abuse. Rather, I believe that various research organizations have respective advantages, as well as limitations, and that these different environments are needed to produce diverse viewpoints and related research findings. Still, with these qualifications stated, it seems efficacious to consider those conditions and influences which encouraged and facilitated our social science research at the Lexington Hospital.

During the first half of its existence and during my 6-year tenure the Social Science Section was a part of the Addiction Research Center. It was a decided advantage to be an integral part of this prestigious research center. The advantages were both administrative and intellectual. Administratively, we received adequate financial support on a continuing basis and thus we were able to employ a full-time research staff which did not have regular clinical or teaching duties. Furthermore, most of the day-to-day administrative chores were undertaken by the central personnel of the Addiction Research Center.

Intellectually, we had complete freedom to investigate any aspect of drug-abuse behavior. Indeed, it is my recollection that we only investigated research topics of our own choosing. Beyond this, and probably of more significance, we had the advantage of close collaboration with the basic science orientation of the Addiction Research Center. Not only were the research library and laboratories available to us, but Dr. Isbell, and later Dr. Martin, provided invaluable support and guidance. Where is the scientific evidence for this statement? Why don't (other) social scientists stick to their methods and forget about ideology? These comments were infrequently rendered, but they had a pervasive impact.

This basic science orientation of the Addiction Research Center was coupled with a concern for thoroughness in research design, application and, especially, the development of requisite social science methodology. I recall no pressure for speedy or premature results. Quite the contrary. Both Drs. Isbell and Martin repeatedly suggested that we take our time and build our research program upon a firm scientific base. Whatever compulsion the Social Science staff felt to achieve results and publish was self-motivated.

From Dr. O'Donnell's review of the research papers which were produced in the Social Science Section, it is evident that the Lexington Hospital itself was a significant factor in our research environment. Indeed, it would be difficult to overemphasize the research advantages which we enjoyed by being a part of the hospital, yet not responsible to it (the administrative, spatial and working arrangements vis-à-vis Social Science Section, Addiction Research Center and the hospital were somewhat complex and probably unique). Among the advantages which we had were ready access to medical records on some 50,000 addict patients; this data source was and still is the best compilation of comprehensive medical and social science data pertaining to drug abuse in the world. We had ready access to the hospital population itself; this enabled us to hold extended discussions with drug abusers about topics of mutual interest as well as to collect interview data for our projects. Beyond these quite obvious research advantages, I believe that the hospital itself was a type of natural laboratory. I know that I learned a great deal by daily informal discussions with patients and staff.

There were, of course, limitations or restrictions imposed upon us by the hospital environment too. We tended to be rather isolated from the mainstream of University and Medical Center affairs. The hospital routine and regulations were often felt to be frustrating. And the prison atmosphere affected some staff adversely. The requirement that papers be subjected to a clearance procedure was sometimes a difficulty (but often an advantage).

Finally, in considering advantages and limitations of the Lexington Hospital environment, it should be mentioned that our social science research program was primarily directed toward drug-abuse patients in treatment (or those who had been in treatment). This limitation had both obvious drawbacks and definite scientific advantages. The shortcomings were that we primarily saw drug abusers when they sought or were compelled to obtain treatment. In addition, we did not, ordinarily, have an opportunity to study those who were not incarcerated.

But I believe that the corollary research advantages involved in focusing upon patients far outweighed the limitations, for the hospital population of thousands of drug abusers provided us with a firm scientific and intellectual base for our developing social science knowledge of drug-abuse behavior. We had unparalleled medical and demographic data on a national population of drug abusers. This enabled us to build a body of knowledge which had special characteristics: (1) It was national in scope, (2) it covered a 40-year span, (3) it was based upon objective data (demographic information, physical examination, laboratory tests, direct interviews, psychiatric diagnosis, drug abuse history, criminal history, and similar data).

In concluding this brief consideration of an optimal environment for drug abuse research, I have two recommendations as to how such research might be further encouraged in the United States.

First, it seems evident that a comprehensive analysis and review of what type of institutional environment fosters particular types of research is needed. Such an analysis should classify research environments into such categories as: (1) University research centers or departments, (2) medical schools and institutes, (3) city or State drug-abuse agencies, (4) Federal agencies, (5) private corporations, (6) drug-treatment programs, (7) foundation supported organizations such as the Drug Abuse Council. These diverse organizations should be studied with respect to the specific type of research output (if any) which they are most capable of producing. For example, which research environment or organization is most capable with respect to basic research, methodology, surveys, new theories, followup studies, clinical finding, or policy-oriented studies. More than a single study is needed to provide these answers as conditions and research priorities change. What is needed is ongoing independent analysis of how particular results can best be obtained.

Second, I recommend that serious consideration be given to the reestablishment of a Social Science Section in the Addiction Research Center. Such a new commitment to basic social science research would, I believe, be instrumental in effecting a significant synthesis and advance in our continuing quest for answers about the behavioral etiology and consequences of drug abuse.

Dr. William R. Martin, *Director,*
Addiction Research Center, 1963–present

Addiction Research Center, 1963–75: Neuropharmacology and Neurochemistry

William R. Martin, M.D., M.S., Jewell W. Sloan, B.S., and Charles G. Eades

I joined the staff of the Addiction Research Center in 1957. When Dr. Isbell interviewed me for a position as neuropharmacologist, I told him that I wished to continue my studies on the role of neurotransmitters in CNS function. I had a thing about norepinephrine and chlorpromazine in those days and knew little about drug abuse. He said "fine" and I was given a back laboratory in the old animal building (figure 1). I appropriated Dr. Wikler's Offner EEG and frequency analysers. Charles G. Eades joined me, and we began a long collaboration and friendship. Among our early accomplishments were obtaining the first window

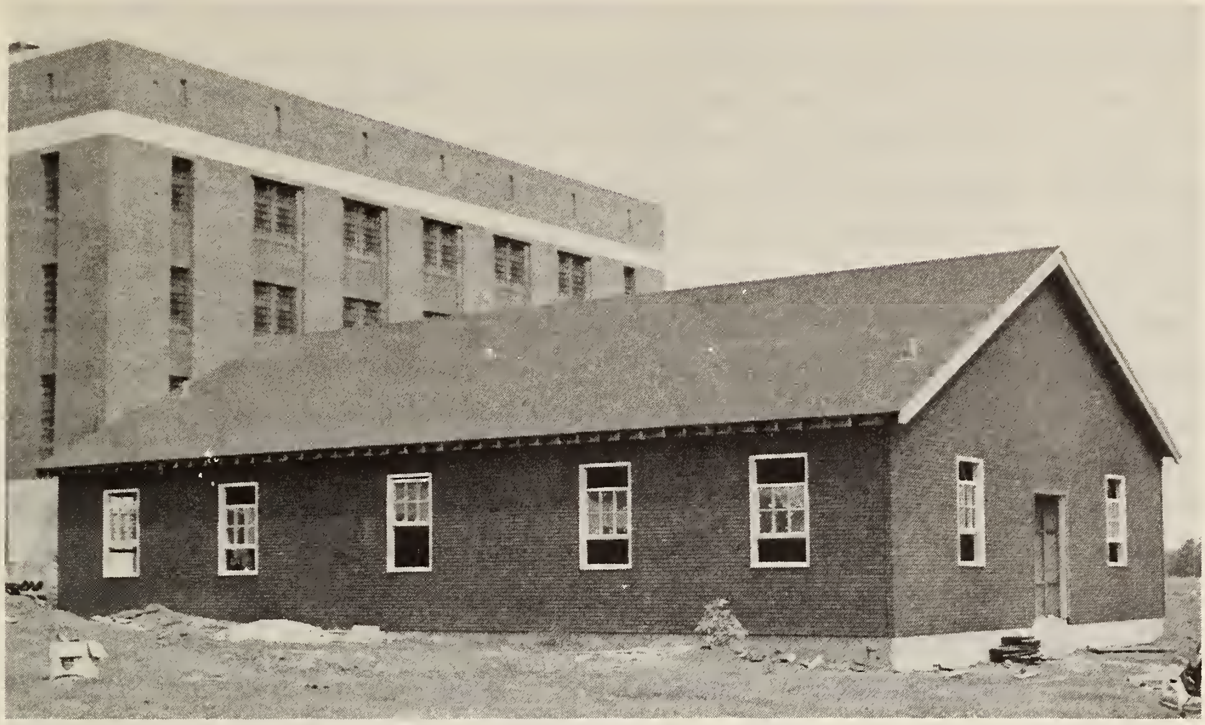

FIGURE 1. *The old animal house of the Addiction Research Center. This temporary structure was erected in 1951 and was demolished in 1965. During this time, it served as a basic research facility for the Addiction Research Center and most of the animal studies on the neuropharmacology of barbiturate dependence were conducted in this building.*

air-conditioner in the old animal building and gaining control of the water heater room for our spinal dogs, a preparation which I also appropriated from Dr. Wikler. During the early years, I had complete freedom to experiment and think. It was during these years that much of my thinking about the mode of action of narcotics and mechanisms of tolerance and dependence was formulated.

In 1959 while Dr. Isbell was on sabbatical leave, Dr. Fraser invited me to collaborate with him on some experiments on the ward. I became very much involved in using questionnaires for studying subjective drug effects, techniques that were pioneered by Henry Beecher, Ray Houde, Harris Isbell, Harris Hill, and Frank Fraser. In 1960, Dr. Anna J. Eisenman, Jewell W. Sloan, and I began a collaboration which continued to Dr. Eisenman's retirement and to the present time with Mrs. Sloan. We extended work in neurochemistry into the catechol- and indoleamines.

About a year or two before Harris Isbell retired, I began to help in the planning of the basic research building with the hope of expanding the neuropharmacology program. Near the time of Dr. Isbell's retirement, we found that available funds were not sufficient to build the basic research laboratory we had planned. We quickly redesigned the building and, although it did not have all of the facilities the staff desired, the new structure was an improvement over the old one and was occupied in

1965 (figure 2). About that time, the plans of Drs. Isbell, Wikler, and Fraser to retire became known.

I assumed the directorship of ARC in 1963. It has been my good fortune to have had the support of Drs. John Eberhart, Gian Salmoiraghi, Sherman Kieffer, Sidney Cohen, Harold Conrad, William Bunney, and William Pollin during my tenure as director. A simple calculation will reveal that my supervisors lasted on the average about 2 years. Lest unwarranted conclusions be read into this statistic, it should be pointed out that the years 1963 to 1975 have been years of vigorous, sometimes hectic, growth for drug addiction, characterized by frequent reorganizations. The ARC has received strong fiscal support, and there have been few worthwhile and relevant experiments deferred because of lack of funds or personnel. The ARC was also encouraged and supported by Dr. Jerome Jaffe and Special Action Office for Drug Abuse Prevention (SAODAP).

During these years, there have been a large number of administrative changes. In 1967, the ARC was transferred from the intramural program of NIMH to the newly formed Division of Special Mental Health Research. When the Division of Narcotic Addiction and Drug Abuse was established in 1968, the ARC was transferred to it. With the passage of the Narcotic Addict Rehabilitation Act (NARA) and the transfer of the hospitals at Lexington and Fort Worth to NIMH and the establishment of the Clinical Research Centers, the admission of Federal prisoners to these institutions was discontinued. A memorandum of understanding was negotiated between NIMH and the Bureau of Prisons permitting the transfer of Federal prisoners to the ARC for participation in research studies. The first prisoner was transferred from the Atlanta Penitentiary July 24, 1968. Over the ensuing years, the ARC developed its own prisoner unit including a prison industry, the print shop. In late

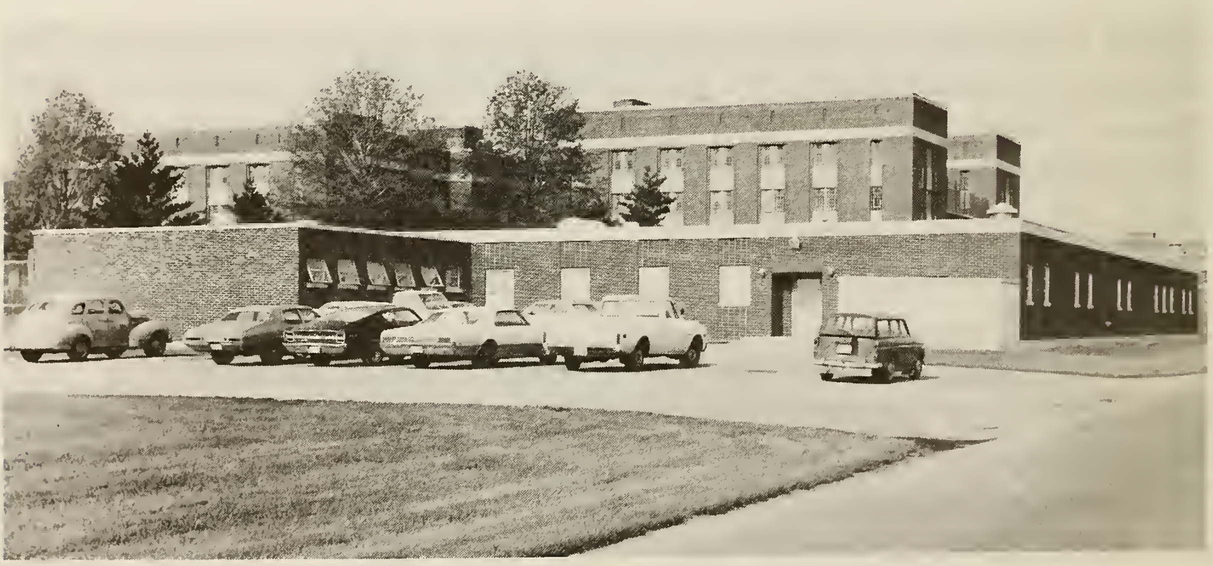

FIGURE 2. *The Basic Research Laboratory of the Addiction Research Center, which was occupied in 1965.*

1973, NIDA was established and the ARC became a branch in the Division of Research. In February 1974, the Lexington Clinical Research Center was closed and the facility turned over to the Bureau of Prisons. At this time, the ARC's administrative autonomy increased.

When Drs. Isbell, Wikler, and Fraser retired in 1963, the ARC lost at the same time three of its most prestigious investigators. This occurred at a time when there was vigorous competition for both medical and scientific personnel. It has been my good fortune to have a number of extremely talented young investigators join the staff of the ARC. Some have remained at the ARC, others have left for additional training, and all have continued to be valued members of the medical, academic, and scientific community. Those who have joined me in a collaborative relationship and have contributed much to the success of our experiments are C.W. Gorodetzky, T.K. McClane, D.R. Jasinski, J.D. Sapira, R.D. Hoeldtke, P.A. Mansky, D.B. Vaupel, J.A. Bell, V.L. Sandquist, P.E. Gilbert, Barbara Hewett, L.G. Sharpe, Masako Nozaki, and W.B. Pickworth.

As a consequence of the rapid expansion of and changes in the nature of the Federal drug-abuse program, the process of administering the ARC has been somewhat turbulent. I have never abandoned my desire to continue as a "bench" scientist. Having to become involved in administrative affairs, occasionally in policy decision, at times serving as an advocate for clinical experimentation and the biomedical approach to drug addiction, and finally in facilitating the growth and transformation of a laboratory frequently were viewed as distractions and the assumption of responsibilities as an annoyance. These distractions and annoyances, however, have had the irritating property of revealing new and interesting problems, broadening interests and taking me into scientific problems that I would have, if left to my own devices, avoided. After having been immersed in problems related to drug addiction and criminality for well over a decade, I have slowly come to realize that it is a unique and yet fundamental type of neuro- and psychopathology which is among the most important, if not *the* most important, of all mental health problems.

Neurochemistry and neuropharmacology have had a long and rich tradition at the Addiction Research Center, and I will attempt to summarize the accomplishments that have been made in these areas, excepting only electroencephalographic studies which will be covered by Dr. Kay, and studies of the neuropharmacology of barbiturate dependence which are treated in Dr. Isbell's presentation.

Wikler and his collaborators adopted Sherrington's spinal dog preparations and conducted extensive studies in which they made two fundamental groups of observations. Wikler demonstrated that morphine and related drugs depressed the flexor reflex and crossed extensor reflex of the chronic spinal dog but did not affect the patellar and enhanced the ipsilateral extensor thrust reflex. Wikler and Frank [55] then demonstrated that when morphine and methadone were administered chronically, tolerance developed to these effects and that when morphine was withdrawn spinal cord signs of abstinence emerged which were manifest by facilitation of the flexor and crossed extensor reflex and the emergence of hind-limb stepping movements. These experiments demonstrated that morphine was not a general CNS depressant but exhibited selectivity of action even at the spinal cord level and with the observation that the decorticate dog could be made dependent on morphine and methadone [53] clearly demonstrated that the abstinence syndrome was a consequence of altered central nervous excitability, physical dependence. In another group of studies Houde and Wikler [15] and Houde et al. [16] studied a number of centrally acting drugs including pentobarbital, interneuron depressants, and morphine, and showed that each of these drugs differed from the other in the pattern of central nervous system alterations that they produced, and were among the earliest neuropharmacologists to point out that drugs that affect the central nervous system have diverse effects and that these syndromes of diverse effects can assist in classifying centrally acting drugs. Wikler and Carter [54] demonstrated that nalorphine precipitated an abstinence syndrome in the dependent chronic spinal dog, that signs of precipitated abstinence were mediated by the central nervous system both above and below the level of transection, and that spinal cord precipitated abstinence closely resembled withdrawal abstinence seen in this preparation. Wikler's interest then turned primarily to problems of psychopharmacology and electroencephalography. Neuropharmacologic studies were continued by Carl Essig, whose interests were primarily related to barbiturate dependence.

The first experiments that I conducted at the Addiction Research Center were continuations of ones initiated at the Department of Pharmacology at the University of Illinois, concerning the role of norepinephrine and ACh in the mediation of the arousal and EEG activating response and descending vasomotor responses [25]. In these studies, we showed that both chlorpromazine, a drug which antagonizes several neurotransmitters, and atropine, a drug that is relatively selective in blocking the effects of acetylcholine, elevated the electrical threshold of the mesencephalic centers which evoked EEG activation and vasopressor responses but that the effects of these antagonists could be surmounted by increasing stimulus strength. The doses of the antagonists were such that we felt it was highly unlikely that endogenous release of acetycholine or norepinephrine could have surmounted the blockade and concluded that these ascending and descending pathways must consist of parallel pathways, each employing several neurotransmitters. We termed this arrangement "pharmacologic redundancy." Figure 3 illustrates this principle. It occurred to us that this type of neuronal pattern and function might be a mechanism which could give rise to tolerance and dependence on morphine, as well as other depressant drugs. If one of the pathways was depressed by a drug, the parallel pathway could hypertrophy, thus causing tolerance. When the drug was withdrawn, the final common pathway would be hyperexcitable as a consequence of the addition of central excitatory effect of the hypertrophied pathway with that of the released morphine-sensitive or depressed pathway.

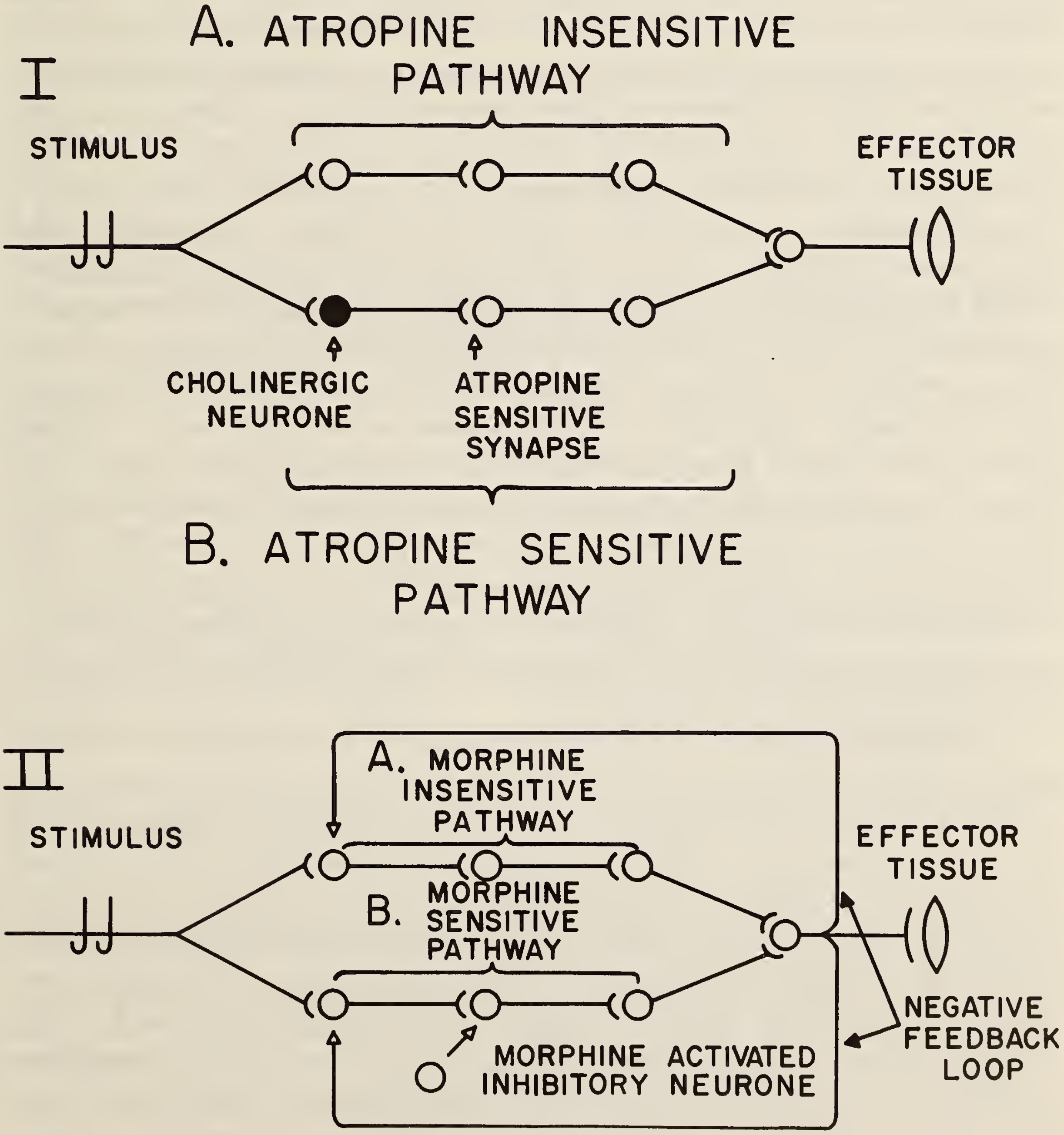
A. ATROPINE INSENSITIVE PATHWAY
I
STIMULUS
EFFECTOR TISSUE
CHOLINERGIC NEURONE
ATROPINE SENSITIVE SYNAPSE
B. ATROPINE SENSITIVE PATHWAY
II
STIMULUS
A. MORPHINE INSENSITIVE PATHWAY
EFFECTOR TISSUE
B. MORPHINE SENSITIVE PATHWAY
NEGATIVE FEEDBACK LOOP
MORPHINE ACTIVATED INHIBITORY NEURONE

FIGURE 3. *A schematic drawing indicating the principle of pharmacological redundancy and the hypothetical conditions necessary for the development of tolerance and dependence (see Martin* [23]*for explanation). Reproduced from Martin* [23].

Our interests then turned to the phenomena of acute tolerance and physical dependence. Schmidt and Livingston [46, 47], and Wikler and Carter [54] had previously shown that both tolerance and physical dependence could be induced by a single dose of a narcotic. We found that both tolerance and physical dependence as manifested by precipitated abstinence could be reproducibly induced by a single 8-hour infusion of morphine in the intact and in the chronic spinal dog [26, 27]. It was during these studies that we first became aware of the complexity of the true nature of tolerance and the problems associated with its measure and became interested in the role of homeostatic mechanisms in the genesis of certain signs of both acute and physical dependence. Himmelsbach [14] had suggested that morphine altered hypothalamic homeostats and that in response to these alterations contra-adaptive reactions occurred which gave rise to tolerance. When morphine was withdrawn the persistence of these contra-adaptive influences in conjunction with the disinhibited centers gave rise to signs of physical dependence. In several studies conducted in collaboration with Dr. Anna Eisenman, we were able to show [23, 24, 32] that indeed homeostatic influences did play a role in both acute and chronic physical dependence for certain but not all physiologic variables. In acute physical dependence, some but not all signs of precipitated abstinence could be accounted for by morphine's depression of the respiratory and temperature homeostats and signs of precipitated abstinence were a consequence of the rapid resensitizing of these homeostats which were confronted by a markedly altered internal milieu (figure 4A–D). When the body rectified the disturbance in the internal milieu, the signs of precipitated abstinence disappeared; however, in chronically dependent man we found that indeed the respiratory homeostat itself was hypersensitive to carbon dioxide [38]. The homeostatic theory of tolerance and dependence is presented in figure 4.

In 1960 Jewell Sloan, Anna Eisenman, and I undertook a series of experiments that in one form or another have continued to occupy us until the present. In our first studies, we studied the relationship of brain catecholamines to various physiologic functions in the rat and found that morphine in a dose-related manner depressed body temperature and motor activity and increased brain catecholamine levels but did not alter brain serotonin levels. Thebaine, on the other hand, produced convulsions and a modest decrease in brain and heart catecholamine levels. We then studied the effects of chronic morphine administration on tissue weights and catecholamine levels and found that chronic morphine administration produced adrenal hypertrophy and increased brain levels of catecholamine but did not affect brain levels of serotonin. Upon withdrawal it was found that brain and heart levels of catecholamines were decreased [48], and there was an increase

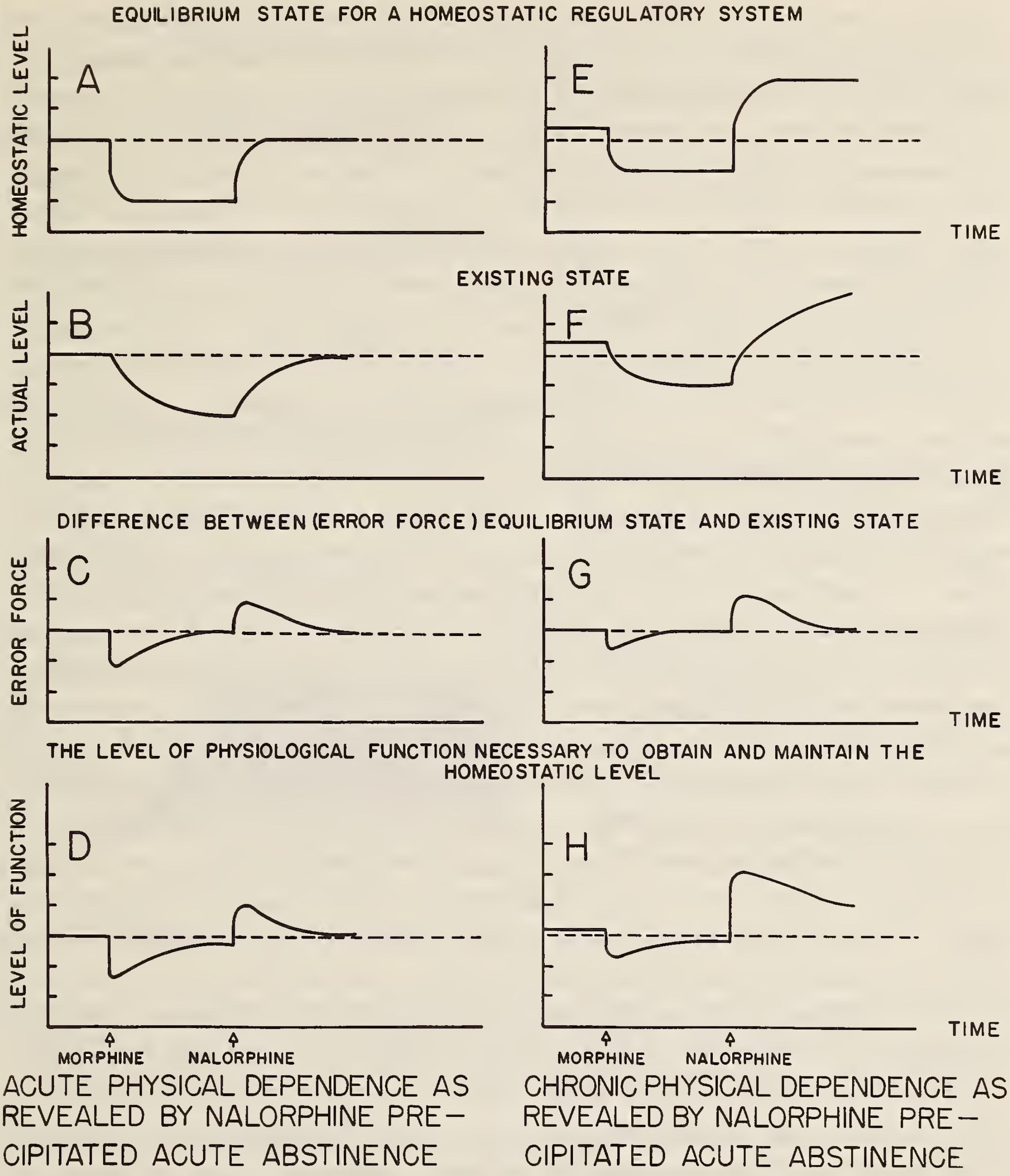

FIGURE 4. *A general and theoretical formulation of the homeostatic theory of acute and chronic tolerance and physical dependence. Reproduced from Martin* [23].

in urinary epinephrine, norepinephrine, and possibly dopamine excretion [49]. However, all of these changes did not covary together [50].

In an attempt to understand some of these disparities in time action, a study was undertaken with Dr. Wikler to reexamine the process of physical dependence in the rat with particular emphasis on time course of the emergence of the abstinence syndrome [43]. In these studies we found that the abstinence syndrome had two phases, an early phase characterized by a loss of weight, a decrease in body temperature and metabolic rate and activity, and a marked increase in "wet dog" shakes. This syndrome persisted for less than a week and was then followed by a syndrome of quite a different character in which the abstinent rats gained body weight more rapidly than control rats, had an increase in fluid intake, a modest increase in "wet dog" shakes, a marked increase in body temperature and metabolic rate, and increased activity. The early changes were called "early" or "primary" abstinence and the changes that appeared after the first week "secondary" or "protracted" abstinence. Subsequently, we studied the effects of prolonged morphine administration and withdrawal in man and the dog [4, 31, 36, 38]. We found that in man there was also an early abstinence syndrome which had characteristics that had been previously described by Himmelsbach, and which persisted for approximately 1 to 2 months. At this time patients essentially returned to their control state, but thereafter exhibited a syndrome which was different from their control state or state that they exhibited while chronically intoxicated with morphine. We subsequently studied a number of changes that were associated with intoxication to methadone and the long-term effects of withdrawal [37]. Essentially, these studies indicate that the primary abstinence syndrome lasts for 1 to 2 months and is followed by a protracted abstinence syndrome, which is characterized by modest decreases in blood pressure, heart rate, body temperature, and pupillary diameter; a decreased sensitivity and responsivity of the respiratory center to carbon dioxide; and a trend for the patients to sleep more and for them to have hypophoric feeling states. These changes persisted as long as we studied the patients, which was 7 months after total withdrawal from morphine (figures 5 and 6). Although protracted abstinence in the dog and rat has different characteristics than it does in man, we have not seen complete recovery in either of these species. Our studies in the dog have indicated that the dog is hyporesponsive to mildly nociceptive stimuli and hyperresponsive to strongly nociceptive stimuli during protracted abstinence. These findings are in agreement with those of Himmelsbach [13] who found that morphine-dependent subjects exhibited hyperresponsivity to the cold pressor tests for many months after their withdrawal.

O'Donnell [45] found that addicts' levels of social adjustment following their first addiction were never as good as they were prior to their becoming addicted. We have obtained, I believe, solid evidence that processes that may have been psychiatric manifestations and which may predispose the addict to drug abuse, may be worsened as a consequence of their having been made physically dependent and that these changes may have a very long persistence.

Our efforts to gain clues concerning the neuronal events that are responsible for morphine's action as well as for a development of physical dependence and the emergence of the phenomena of early and protracted abstinence have taken several courses. We have developed a model using the chronic spinal dog that measures many of the

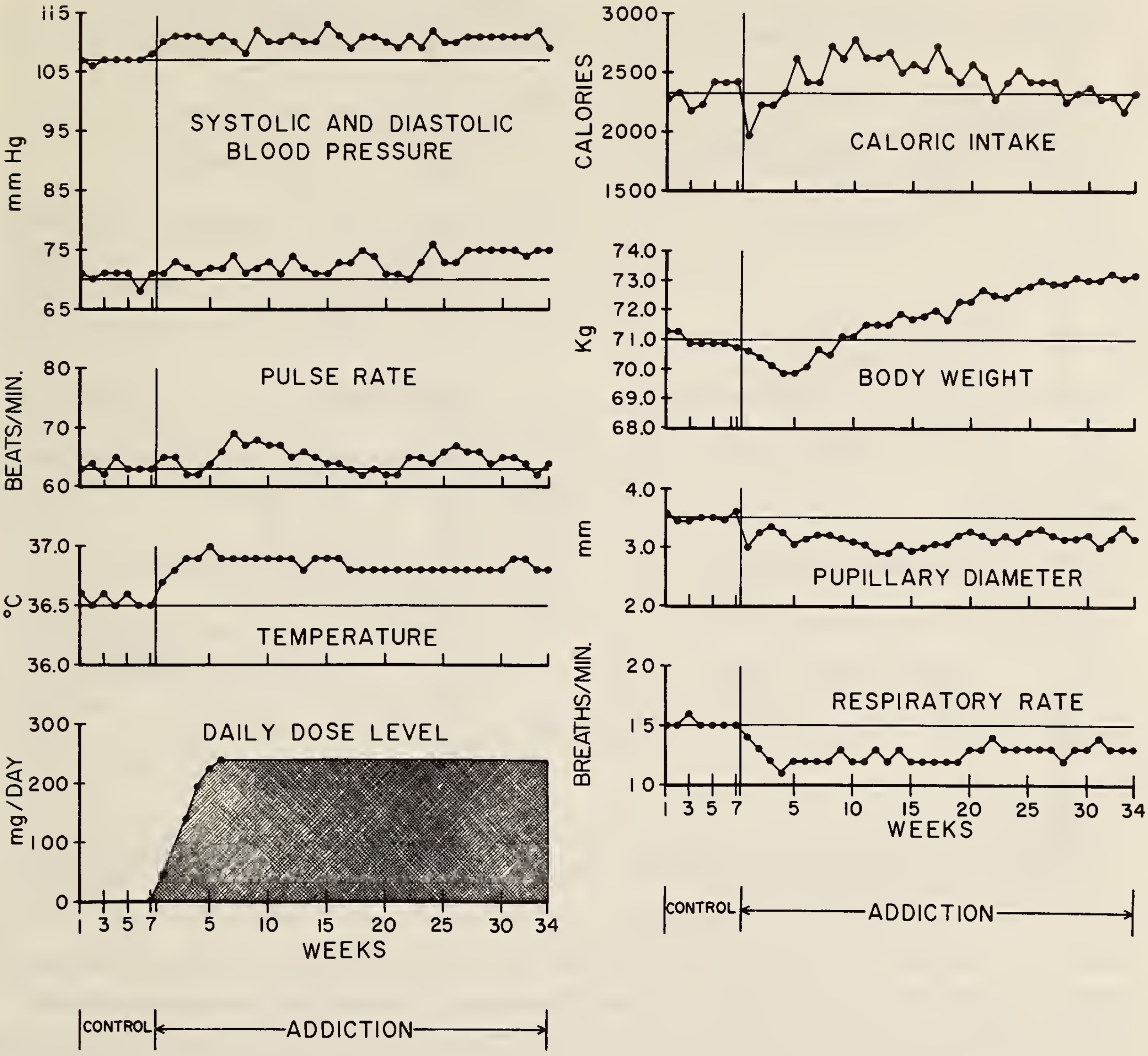

FIGURE 5. *The effects of chronic administration of morphine on clinical variables, Each point represents the weekly mean a.m. observations for seven subjects. The horizontal line represents the mean of control determinations for seven subjects. Reproduced from Martin and Jasinski* [36].

physiologic parameters that are also measured in man, which has allowed us to assess quantitatively not only a number of physiologic actions of narcotics in the nondependent dog such as analgesia, mydriasis, effects on body temperature, etc., but to measure the precipitated and withdrawal abstinence and to assess the ability of a variety of agents to suppress and precipitate the abstinence syndrome (table 1). In the course of these studies, we have found that a number of agents such as methoxamine, a noradrenergic agonist, tryptamine, oxotremorine, a muscarinic agonist, amphetamine, and 5-hydroxytryptophan all mimic to one degree or another the morphine-abstinence syndrome in the spinal dog; however, the use of appropriate antagonists such as phenoxybenzamine, chlorpromazine, atropine, and cyproheptadine which almost completely antagonize the agonistic action of these mimickers of neurotransmitters, produces at best a partial suppression of the morphine abstinence syndrome. We have been forced to conclude that

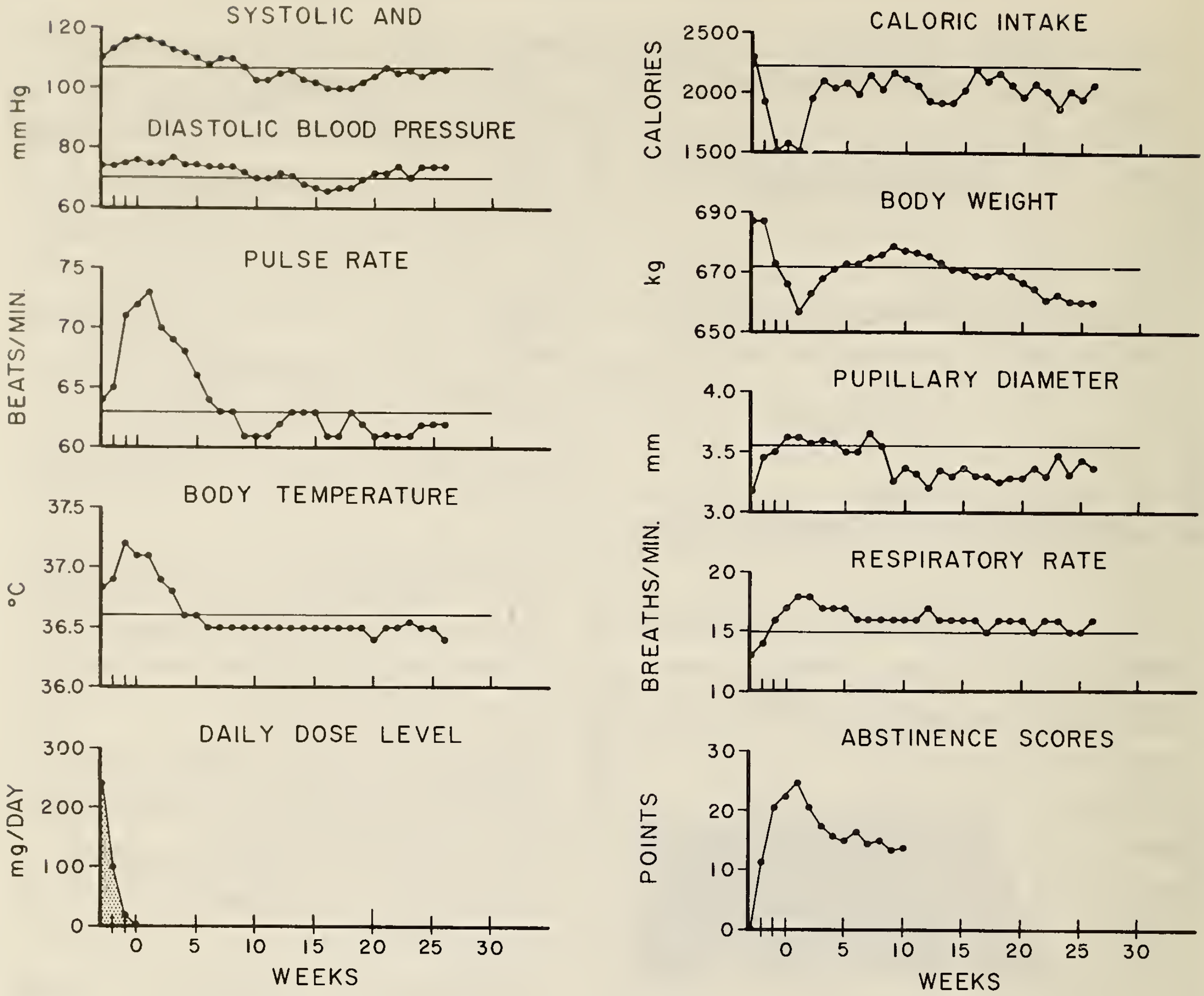

FIGURE 6. *Changes seen during early and protracted abstinence. Each point represents the mean weekly a.m. values for six subjects. The first point of each curve represents the mean value for the last 7 weeks of addiction. The horizontal line represents the mean control value for the six subjects. One subject was withdrawn from the study near the end of the chronic intoxication phase because of episodes of acute colecystitis. Reproduced from Martin and Jasinski* [36].

these agonists are neither responsible for the primary actions of morphine nor are they primarily responsible for the abstinence syndrome.

Yet another approach to this problem has been through the study of polypeptides. Krivoy and his collaborators [1] were the first to show that agents that inhibited protein synthesis prevented the development of tolerance. Krivoy et al. [20] and Zimmermann and Krivoy [56] have shown that morphine depresses both the mono- and polysynaptic reflex in the acute spinal cat and in the isolated frog spinal cord. Krivoy et al. [19] have shown that β-melanocyte-stimulating hormone and tetracosactin antagonize the effects of morphine on the segmental reflex and Zimmermann and Krivoy [56, 57] have shown that tetracosactin antagonized the effects of morphine on the isolated frog spinal cord. Further, Krivoy et al. [21] have shown that desglycinamide^9-lysine vasopressin, which does not have activity in its own right, facilitates the development of tolerance to morphine. There is an increasing body of evidence that there may be endogenous polypeptides in the central nervous system and peripheral tissue that are some way related to the

TABLE 1. *Mean precipitation and suppression scores of two groups of dogs dependent respectively on 54 and 125 mg/day. Reproduced from Martin et al.* [31].

			Precipitation Abstinence						Suppression of Withdrawal Abstinence	
			54 mg/day			125 mg/day			54mg/day	125mg/day
			I	II	T_{54}	I	II	T_{125}	W_{54}	W_{125}
GRADED SIGNS										
YAWNING		[1]	21.2 (13)	20.0 (12)	20.7 (11)	20.5 (15)	11.2 (9)	18.5 (11)	- 3.3 (14)	- 7.4 (9)
LACRIMATION		[2]	16.6 (17)	11.6 (11)	18.7 (14)	21.0 (14)	4.0 (15)	12.4 (14)	-21.9 (5)	-13.6 (6)
RHINORRHEA		[1]	20.3 (14)	19.4 (14)	19.8 (12)	19.0 (16)	2.3 (16)	10.7 (16)	-13.4 (11)	-12.6 (7)
SALIVATION		[2]	1.4 (20)	11 6 (18)	6.5 (20)	13.6 (18)	-8.0 (21)	2.8 (21)	-37.8 (2)	-39.1 (1)
TREMOR		[1]	24.5 (10)	13.4 (16)	18.9 (13)	17.4 (17)	1.6 (18)	10.0 (17)	-15.6 (8.5)	- 9.4 (8)
RESTLESSNESS		[1]	29.8 (7)	27.1 (9)	28.4 (7)	22.3 (13)	8.3 (13)	15.3 (13)	-13.7 (10)	-13.7 (5)
WHINING		[2]	17.5 (15)	13.2 (17)	15.4 (16)	31.0 (10)	5.4 (14)	18.2 (12)	- 1.2 (15)	- 2.9 (13)
PRESENT OR NOT										
GNAWING		[2]	32.3 (6)	33.3 (6)	32.8 (6)	56.5 (6)	48.0 (4)	52.2 (4)	- 0.6 (17)	- 6.0 (10)
HEAD TOSSING		[2]	21.3 (12)	9.0 (19)	15.2 (17)	7.5 (20)	0.5 (19)	4.0 (19)	- 4.9 (13)	- 2.1 (15)
BARKING		[10]	16.7 (16)	20.0 (13)	18.3 (15)	35.0 (8)	10.0 (10)	22.5 (9)	0 (19.5)	0 (18.5)
PILOERECTION		[10]	38.3 (5)	45.0 (5)	41.7 (5)	65.0 (4)	8.8 (11)	36.9 (6)	0 (19.5)	0 (18.5)
RETCHING		[50]	8.3 (18)	16.7 (15)	12.5 (18)	125.0 (1)	162.5 (1)	143.8 (1)	0 (19.5)	0 (18.5)
EMESIS		[50]	0 (21)	0 (21)	0 (21)	31.5 (7)	12.5 (7)	25.0 (8)	0 (19.5)	0 (18.5)
URINATION		[1]	22.8 (11)	21.0 (10)	21.9 (10)	26.4 (12)	12.1 (8)	19.2 (10)	- 0.7 (16)	- 0.4 (16)
PANTING		[4]	27.3 (18)	27.5 (8)	27.4 (9)	10.0 (19)	8.3 (12)	9.2 (18)	-15.6 (8.5)	- 2.5 (14)
STEPPING (Frag.)		[1]	5.8 (19)	8.5 (20)	7.2 (19)	5.2 (21)	1.5 (17)	3.4 (20)	- 7.7 (12)	- 4.6 (12)
STEPPING (Cont.)		[3]	26.5 (9)	29.5 (7)	28.0 (8)	33.0 (9)	34.5 (5)	33.8 (7)	-17.4 (7)	- 5.8 (11)
MEASURABLE SIGNS										
TEMPERATURE	{.1°C}	[10]	68.8 (2)	74.2 (3)	71.5 (2)	99.2 (3)	73.0 (3)	86.1 (3)	-45.3 (1)	-26.0 (3)
RESPIRATION	{1br/min}	[.1]	61.2 (3)	67.6 (4)	64.4 (4)	30.2 (11)	-6.2 (20)	12.0 (15)	-29.9 (4)	-28.2 (2)
PULSE	{1b/min}	[.1]	85.9 (1)	112.0 (2)	98.9 (1)	100.7 (2)	76.2 (2)	88.4 (2)	-37.3 (3)	-22.7 (4)
PUPILLARY DIAMETER	{1mm}	[2]	55.0 (4)	74.8 (1)	64.9 (3)	64.2 (5)	13.0 (6)	38.6 (5)	-17.9 (6)	17.2 (21)

morphine receptor. Although there have been reports that Substance P will suppress the abstinence syndrome in the rat, studies in the chronic spinal dog with synthetic Substance P indicate that this polypeptide is inactive.

Work at the Addiction Research Center has indicated that indeed there are several receptors in the central nervous system that must be closely related to the morphine receptor in their steric configurations. In our early studies we showed that the activity of both cyclazocine and nalorphine in producing not only agonistic effects but physical dependence was characteristically different from morphine's agonistic activity (table 2) [33, 34]. On the basis of these findings, kinetic data of Dr. Houde, as well as findings that indicated that the agonistic effects of cyclazocine were more resistant to the antagonistic effects of naloxone than were the effects of morphine, we concluded that there were two distinct receptors that were respectively responsible for morphine's and cyclazocine's agonistic activities [22]. Subsequent studies showed that naloxone was more effective in antagonizing the convulsant effects of heroin or propoxyphene than it was in antagonizing the effects of thebaine, suggesting that there are at least two receptors and two mechanisms involved in the convulsions produced by these drugs [6]. Finally, in the study of a series of analgesics that had varying degrees of psychotomimetic, sedative, and analgesic activity in the chronic spinal dog, we have accumulated evidence that there are at least three receptors, a morphine (μ), a ketocyclazocine (κ) and a SKF–10,047 (σ) receptor each of which is distinguishable on the basis of its pharmacologic

TABLE 2. *The relative percentage and rank of various sources of "Himmelsbach" points for morphine, cyclazocine, and nalorphine abstinence syndromes.*

The values for morphine and cyclazocine have been previously reported [33]. *The values for nalorphine were calculated from data obtained from the seven experimental subjects reported in this paper* [34]. *Spearman correlation coefficients* (r_s) [52] *for the various conditions are also indicated. The values in parentheses indicate the level of significance for the various correlations. Reproduced from Martin and Gorodetzky* [34].

	MORPHINE		CYCLAZOCINE		NALORPHINE	
SOURCE OF POINTS	% OF TOTAL POINTS	RANK	% OF TOTAL POINTS	RANK	% OF TOTAL POINTS	RANK
+ SIGNS	4.4	6	12.8	4	11.0	3
+ + SIGNS	9.3	5	16.7	2	3.8	7
CALORIC INTAKE	1.9	8	5.5	6	6.7	6
RESTLESSNESS	0.8	9	0	9	1.1	8
EMESIS	2.8	7	0.7	8	0	9
FEVER	12.3	3	33.9	1	35.8	1
HYPERPNEA	31.1	1	11.1	5	10.8	4
SYSTOLIC B.P.	25.5	2	3.1	7	9.9	5
WEIGHT LOSS	11.5	4	15.8	3	20.9	2

$r_{S_{M \times C}} = .47 (> .05)$ $r_{S_{M \times N}} = .60 (> .05)$ $r_{S_{C \times N}} = .72 (< .05)$

M = MORPHINE N = NALORPHINE C = CYCLAZOCINE

activity and all of which have actions that can be antagonized by naloxone (table 3). We have further acquired a large body of data in the chronic spinal dog [7, 30, 44] and in man [17] that there are partial agonists of both the morphine type (μ) and the nalorphine type (κ).

Neurochemistry at the Addiction Research Center has always been closely integrated to not only the clinical program but the neuropharmacologic program. Eisenman et al. [2, 3, 4] first studied the effects of morphine and the abstinence syndrome on corticosteroid excretion in man. They found, that depending on the conditions, that morphine suppressed the release of corticosteroids, that with chronic administration of morphine tolerance developed to this effect and that when morphine was withdrawn the excretion of corticosteroids may or may not be increased.

Further, it has been shown that chronic methadone administration suppresses secretion of gonadotropins and that during early physical dependence their release may be enhanced.

Following the observations that tryptamine mimicked the activity of LSD, psilocybin, mescaline, DOM, and methysergide on the reflexes of the chronic spinal dog, it was postulated that LSD was acting as a tryptaminergic agonist [28]. Subsequent studies showed that tryptamine's activity in man was similar to that of LSD [39] and that dogs made tolerant to LSD were cross-tolerant to tryptamine [29]. In a long

Table 3. *Characteristics of agonists of the μ, κ and σ type in the chronic spinal dog and the postulated characteristics of mixed agonists.*

	μ MORPHINE	κ KETOCYCLAZOCINE	σ SKF 10047
PULSE RATE	↓	0	↑
PUPILS	↓	↓	↑
RESPIRATORY RATE	↑–↓	0–↓	↑
TEMPERATURE	↓	0?	↑
FLEXOR REFLEX	↓	↓	↓
SKIN TWITCH	↓↓	↓	0
SUBJECTIVE EFFECT IN MAN	EUPHORIA	SEDATION AND DRUNKENNESS	DYSPHORIA AND HALLUCINATIONS
	μ	κ	σ
PENTAZOCINE	HA La	LA Ha	LA Ha
CYCLAZOCINE	HA L or Oa	HA Ha	HA Ha
NALORPHINE	HA L or Oa	LA La	LA La
DIPRENORPHINE	HA L or Oa	HA La	HA La
OXILORPHAN	HA L or Oa		HA La
WIN 35,197-2	LA L or Oa	HA Ha	?
BUPRENORPHINE	HA La	?	?

HA – HIGH AFFINITY
LA – LOW AFFINITY
Ha – HIGH INTRINSIC ACTIVITY
La – LOW INTRINSIC ACTIVITY

series of experiments, it was shown that tryptamine was present in the brain of the rat, guinea pig, cat, dog, steer, and man [41, 51]. It was further demonstrated that the brain releases tryptamine [40, 51]. Through the use of lesioning experiments we have evidence that there are both ascending and descending tryptaminergic pathways in the brain and spinal cord in the dog [42]. These studies strongly suggest that tryptamine is an agonist in the brain and further that the LSD-like psychotogens exert their effects by acting as agonists on tryptaminergic receptors. Thus, we believe we have obtained the first conclusive evidence of an endogenous neurotransmitter whose activity is similar to the LSD-type hallucinogens.

It is well to remember that Lewin's original studies with mescaline and that Isbell's more recent studies with LSD showed that these substances were euphoriants. It is possible that feelings of well-being may be to a degree dependent on a properly regulated tryptamine metabolism and that when tryptamine is present in subnormal levels, patients may have hypophoric feeling states which may be directly related to the fundamental pathology of the psychopath. Stimulated by the observations of several laboratories that β-phenethylamine is present in the central nervous system and that its structure and its pharmacologic actions are similar to that of another euphoriant, amphetamine, β-Phenethylamine has been studied in the chronic spinal dog and evidence has been obtained that would indicate that phenethylamine is involved in functional systems that are neither noradrenergic nor tryptaminergic in nature. These findings suggest that the brain may have specific phenethylaminergic receptors. Phenethylamine's actions on the spinal cord are antagonized by chlorpromazine but not by phenoxybenzamine or cyproheptadine. It is also known that chlorpromazine produces hypophoric feeling states. Thus, there is the possibility that phenethylamine may also be involved in feelings of well-being and that its absence may result in feelings of hypophoria.

Extending the work and thoughts of Kolb [18], Felix [5], Hill [9], Hill et al. [10, 11, 12] Haertzen and Panton [8] and Himmelsbach [13], we have recently postulated that the primary defect in the addict psychopath is that he is basically a hypophoric individual with increased needs and wants [35]. All drugs of abuse produce feelings of euphoria in certain dose levels and many have been shown to reduce need states. The fact that there may be neurotransmitters that produce euphoria and reduce needs should encourage us in our search for chemotherapeutic agents that may be helpful to narcotic addicts and perhaps alcoholics and criminals, to further help us understand the basic pathology of these diseases and eventually to allow physicians to treat addicts and criminals in a humane and definitive way.

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Clinical Aspects of Opiate Antagonists and Partial Agonists

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For almost 30 years, a large portion of clinical research at the ARC has been devoted to narcotic antagonists. From these studies originated most, if not all, of the current therapeutic uses of narcotic antagonists.

The introduction of nalorphine into study at the ARC originated in a visit of Harris Isbell to the University of Illinois in 1946 where he conferred with Klaus Unna [9, 30]. Dr. Unna, of course, had described the pharmacology, including the morphine antagonist activity, of nalorphine in animals [29]. Shortly, Dr. Isbell, in collaboration with Drs. Fraser and Wikler, initiated a series of clinical and animal experiments with nalorphine [3, 4, 6, 7, 8, 31, 32]. The far-reaching theoretical and therapeutic importance of the results of these experiments as well as the primacy of the contributions made by these investigators is clearly demonstrated in the report Dr. Isbell presented to the NAS–NRC Drug

Addiction Committee in 1952 [6]. The following characteristics of nalorphine had been established by these investigators: (1) In nondependent subjects, nalorphine constricted pupils, depressed respiration, elevated blood pressure, produced sedative and hallucinatory subjective effects which subjects distinguished from those of morphine and elevated thermal pain threshold. (2) In physically dependent subjects, nalorphine did not suppress abstinence but instead precipitated a dose-related abstinence syndrome. (3) In nondependent subjects, nalorphine in single doses blocked the euphoric effect of single doses of morphine. (4) In direct addiction studies nalorphine did not produce morphinelike physical dependence. (5) In patients intoxicated with methadone, nalorphine was a clinically effective antidote for narcotic poisoning. In this regard, Dr. Eddy [1] credits Drs. Fraser and Isbell with the first clinical demonstration of this therapeutic use of nalorphine.

The following year at the 11th meeting of the Drug Addiction Committee, Dr. Isbell, suspecting a clinically useful analgesic action, suggested that Dr. Beecher be asked to include nalorphine alone and in combination with morphine in his clinical analgesic assessment [2]. The subsequent demonstration by Lasagna and Beecher [16], as well as Keats and Telford [15], that nalorphine was a clinically effective analgesic in conjunction with the conclusion of Dr. Isbell and his collaborators that nalorphine was nonaddicting indicated a strategy in the search for a nonaddicting morphine substitute. The acceptance of this strategy resulted in the synthesis and development of numerous morphine antagonists.

From these initial studies of nalorphine by Isbell, Fraser, and Wikler, three therapeutic uses of antagonists were introduced into medicine. These were: (1) As antidotes for poisoning with morphinelike drugs; (2) as diagnostic agents for demonstrating physical dependence on narcotics; and (3) as analgesics of low-abuse potential. It should be emphasized that Dr. Isbell, with the assistance of Dr. Eddy, was probably most responsible for recognizing the therapeutic potentialities of nalorphine and for generating and maintaining scientific and medical interest.

Some 10 to 12 years ago, Dr. William R. Martin recognized and introduced the use of narcotic antagonists as chemotherapeutic agents for narcotic addiction [17, 19, 22, 23, 25, 26]. This concept originated in a series of clinical experiments conducted to assess the abuse potential of cyclazocine [20, 21] which was being developed as an analgesic. Underlying this concept for the treatment of addiction was preceding conceptualization of two mechanisms thought to contribute to drug taking—protracted abstinence, and conditioned abstinence and drug seeking. In the experiments with cyclazocine, Dr. Martin and his collaborators not only established the pharmacological characteristics of cyclazocine important in the treatment for addiction, but also observed and measured effects important to understanding the mode of action of antagonists. In this series of studies they: (1) Determined that nalorphine and cyclazocine produced similar subjective effects and characterized and measured these subjective effects with the single dose questionnaires, (2) determined that a distinct type of physical dependence developed with cyclazocine and nalorphine and that abstinence did not give rise to drug-seeking behavior, (3) determined that cyclazocine was a potent morphine antagonist in man, (4) showed that tolerance developed to the sedative and dysphoric effects of cyclazocine but not to the morphine blocking effects, and (5) demonstrated that chronically administered cyclazocine blocked the euphoria and physical dependence produced by morphine. Thus, cyclazocine was proposed as a pharmacological treatment to block the reinforcing effects of morphinelike drugs and hopefully to allow extinction of protracted abstinence and conditioned drug-seeking behavior.

These studies led to a characterization of the cyclazocine and nalorphine induced subjective state by Dr. Haertzen [5]. Dr. Haertzen found the profile of responses on the Addiction Research Center Inventory to be similar for nalorphine and cyclazocine with this profile clearly distinguished from that of morphine.

In 1965, I joined the ARC and over the next few years collaborated with Dr. Martin in a series of clinical experiments with narcotic antagonists which are of extreme importance to both medicine and theoretical pharmacology [11, 12, 13, 14, 24]. Two factors contributed to the success and importance of these experiments. One was the availability of a large number of new antagonists for clinical study; the other was the intellectual endeavors of Dr. Martin to understand the relation between the effects of the antagonists alone and their morphine antagonist activity and to understand the mechanism of tolerance and dependence.

The first antagonist assessed was naloxone [11] which alone was indistinguishable from placebo since it produced no subjective or physiologic effects upon acute or chronic administration or upon abrupt withdrawal. Yet naloxone was a potent antagonist to morphine. In these experiments it was recognized that naloxone was a pure antagonist of theoretical and practical importance. These experiments more than any others were responsible for the introduction of naloxone into clinical practice.

In this period Dr. Martin had already formulated a number of hypotheses which were to underlie this series of experiments [13, 18, 24]. First, the subjective and physiologic effects of the antagonists alone or their "agonist" effects were separable from their "antagonist" actions. Second, at least two types of receptors are involved in the agonist activity of morphine and nalorphinelike drugs. Third, morphine and nalorphine type drugs could differ in agonist activity. Fourth, in the tolerant dependent subjects these agents continue to exert agonist activity.

In these experiments with naloxone [11], two methodological developments occurred. A procedure was developed for measuring the relative morphine antagonist activity of agents in man. Based on the work of Haertzen [5], subsets of items from the scales of the Addiction Research Center Inventory were utilized to quantitatively measure the subjective effects of the antagonist and to classify agents as morphinelike or nalorphinelike agonists.

Very shortly, it was shown that naloxone, the pure antagonist, would antagonize the agonist effects—miotic, subjective, and respiratory depressant—of cyclazocine, another narcotic antagonist [14]. Thus, naloxone could be used clinically to terminate the toxic psychosis produced by agents such as nalorphine and cyclazocine and to treat the respiratory depression produced by agents such as pentazocine.

During the experiments with naloxone it was obvious that naloxone as a pure antagonist would have advantages over cyclazocine as a chemotherapeutic agent for narcotic addiction. However, naloxone was found to be ineffective orally and of short duration of action. Dr. Martin hypothesized that an antagonist with the 14-hydroxy substitution of naloxone and the N-cyclopropyl methyl substitution of cyclazocine would have appropriate characteristics as a chemotherapeutic agent for addiction. He found that Endo Pharmaceuticals had synthesized this compound as EN1639A, persuaded Endo to obtain an IND, and initiated studies in man in 1969. This compound, naltrexone, was for practical purposes a pure potent antagonist, orally effective and with a duration of action sufficient for use on a once-a-day basis [25].

Another major finding was the demonstration of partial morphine agonist activity in man with profadol and propiram along with the development of a technique to measure the intrinsic activity of morphinelike drugs in man using various levels of morphine dependence [13]. Profadol and propiram produce typical morphinelike euphoria and subjective effects as well as morphinelike physical dependence such that the agonist effects were morphine- rather than nalorphinelike. Yet like nalorphine and cyclazocine, profadol and propiram would not suppress abstinence in subjects dependent upon 240 mg of morphine per day but were effective antagonists and precipitated abstinence. From Dr. Martin's formulations, these were concluded to be partial agonists of morphine. This concept was confirmed when profadol and propiram suppressed abstinence in subjects dependent upon 60 mg per day.

In recent years additional clinical studies with antagonists have produced results of therapeutic and theoretical importance. Nalbuphine is an antagonist with analgesic activity in man which is significantly less psychotogenic than the antagonists pentazocine, cyclazocine, and nalorphine [10]. These results indicate that dissociations of analgesic and psychotomimetic actions can be obtained. Other studies demonstrated the pharmacologic feasibility of adding naloxone to methadone for use in maintenance to lower the parenteral abuse liability of methadone [28]. These studies also indicated that single doses of methadone produced sufficient physical dependence in our subjects such that 1 week later naloxone would precipitate a moderately severe abstinence syndrome. During evaluation of the antagonist oxilorphan as a potential chemotherapeutic agent for narcotic addiction it was observed that in contrast to morphinelike agents, oxilorphan produced a diuresis of urine of low specific gravity even in the face of dehydration [27]. Experiments showed that this effect was a consequence of the agonist actions of oxilorphan and was probably due to inhibition of ADH release. A proposed therapeutic application of this phenomenon now being investigated is the treatment of syndromes of inappropriate ADH secretion.

Currently, narcotic antagonists are still actively being studied in the clinical program of the ARC and hopefully other theoretical and therapeutic contributions will be forthcoming.

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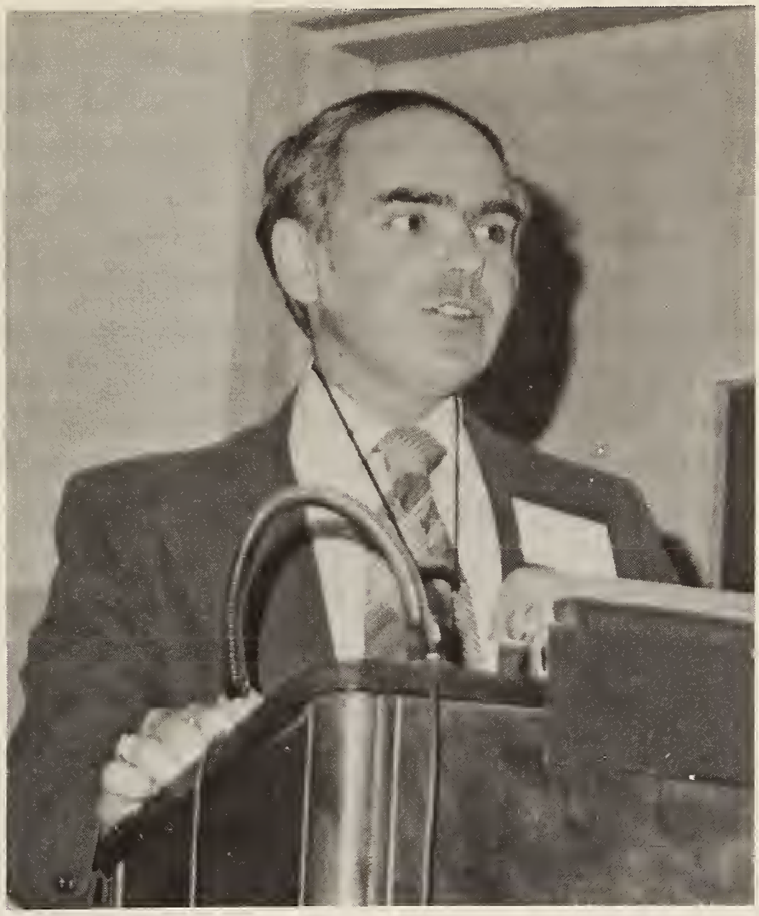

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Biochemical Aspects, Drug Metabolism and Detection

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Over the last 40 years a large number of studies have been performed in the Research Section of the Lexington USPHS Hospital (subsequently the Addiction Research Center) pertaining to the metabolism and detection of drugs of abuse and in biochemical pharmacology. It is the purpose of this paper to review some of those studies which have not been reviewed by other participants in different contexts.

Early Drug Metabolism Studies (1938–44)

Between 1938 and 1944 Oberst and colleagues reported pioneering metabolism studies of morphine, heroin, Demerol, and other opiates [18, 34–42]. An improved method for quantitative and qualitative determination of morphine was described [34] using an organic solvent extraction and a phenol reagent color reaction with a sensitivity of 0.8 μg/ml. Using this method morphine excretion was studied in 24-hour urine samples collected for 2 to 31 days from 29 addicts receiving daily morphine injections ranging from 45 mg to nearly 4.5 grams [35]. Approximately 4.5 percent of the administered dose was found as free morphine and 25 percent was excreted as a bound morphine, which was liberated by acid hydrolysis under severe conditions. After abrupt withdrawal of morphine the drug remained detectable in the urine for 5 to 7 days. In later studies [38] this excretion data was generally confirmed and small amounts of morphine were identified as free in the feces, perspiration, and liver (obtained at autopsy); as free and bound in gastric contents; and as bound in the bile. Morphine was not found in blood or saliva. The morphine conjugate was tentatively identified as the glucuronide [37]. A method to determine Demerol in the urine was also described [39]; and it was found that approximately 10 percent of the administered dose was excreted as Demerol in the urine in 24 hours, with ¾ of that being excreted in the first 7 hours following drug administration. Heroin metabolism was studied in three addicts by determination of urinary morphine excretion during maintenance with morphine and after full substitution with heroin [40]. Approximately the same proportion of free and bound morphine was found in the urine before and after heroin substitution. It was concluded that heroin is probably mainly metabolized to morphine and excreted in the free and bound forms, a finding which was later to be confirmed by many investigators.

Clinical Chemical Studies and Alcohol (1939–68)

During the 15-year period between about 1945 and 1960, there was a decrease in activity in drug metabolic studies. However, during this period a variety of clinical chemistry measurements were followed during several studies of the human pharmacology of opiates and sedative hypnotics. In an early study Williams [43] reported that the blood is hydrated during morphine addiction and that blood concentration is normal in postaddicts. Williams and Oberst [44] later studied two subjects intensively for 2 years during various single-dose and chronic morphine administration conditions with a large number of physiologic and biochemical measures. They reported that during addiction there were increases in body water, water content of the blood, sedimentation rate, carbohydrate intake, and nocturnal activity; there were decreases in body weight, hemoglobin, packed cell volume, pulse rate, basal metabolism, and diastolic blood pressure. Eisenman, working with clinical colleagues, did blood counts, urinalyses, and various clinical chemistry measures (such as fasting blood sugar, bilirubin, NPN and uric acid) during human pharmacologic studies of barbiturates [7, 19] and opiates [8, 20, 21, 23]. No significant drug effects were seen in these measures. Because of the high incidence of abnormal liver function tests seen in postaddicts, Gorodetzky et al. [17] studied changes in SGOT, SGPT, thymol turbidity and cephalin flocculation during the course of experimental chronic morphine administration of 7 to 9 months in 20 subjects. No significant or systematic changes were seen in these measures during the addiction period and it was concluded that abnormal liver-function tests were not due to a direct hepatotoxic effect of the drug.

During this period alcohol metabolism was briefly studied during the classical study of Isbell et al. [22] on the etiology of "rum fits" and "delirium tremens." Blood alcohol levels were measured indirectly and it was shown that levels of less than 50 mg/100 ml were maintained with a daily ethanol intake of 400 to 450 ml if the dose was spread throughout the day. A slight increase in dose caused an increase in blood levels. If that increased intake was maintained blood levels fell, but this could easily be overcome by another small dose increase and the blood levels then remained high. Metabolic tolerance to alcohol then appeared limited and easily overcome. On abrupt withdrawal of alcohol manifestations of abstinence were evident before blood alcohol levels fell to zero.

Biochemical Pharmacology Studies (1966–71)

In the early 1960's interest in studies in drug metabolism and biochemical pharmacology again increased. In the area of biochemical pharmacology Mulé reported three studies on the interaction of opiates and phospholipids in the mid and late 1960's [28, 29, 30]. The effects of morphine and nalorphine alone and in combination were studied on the incorporation of P^{32} and C^{14}-labeled intermediates into various phospholipids in cerebral cortex slices of the guinea pig [28]. Dramatic effects were found from predominantly high doses of these drugs on phospholipid metabolism, some stimulatory and some inhibitory. Morphine and nalorphine had many similar effects when given alone, and nalorphine did not consistently influence the effects of morphine when both drugs were used together. The incorporation of P^{32} into phosphatides in cerebral cortical slices from nontolerant guinea pigs given single doses of morphine, from morphine tolerant and from morphine abstinent guinea pigs was then studied [29]. Stimulation of P^{32} incorporation was found from in vivo morphine in the nontolerant animals 1 and 4 hours following a 40 mg/kg morphine dose, and the tissue was sensitive to greater stimulation of P^{32} incorporation by additional morphine added in vitro. Slices from morphine-tolerant animals showed no effect of in vivo morphine and were much less reactive to in vitro additions of morphine. Tissue from abstinent guinea pigs had returned to normal and in some cases showed very great stimulation of P^{32} incorporation after morphine was added in vitro. Use of C^{14}-morphine demonstrated that the drug was present in both nontolerant and tolerant brains (and in fact was at slightly greater concentration in the tolerant animal). The time course of the effect of single doses of morphine in the nontolerant animal roughly paralleled the brain concentration of the drug. These studies were interpreted as consistent with the possible involvement of a biochemical change in phospholipid metabolism in tolerance. A later study [30] demonstrated that morphine and other narcotic drugs were capable of inhibiting calcium binding to phospholipids, and, therefore, inhibiting the transport of calcium by phospholipids from an aqueous to an organic phase in an in vitro test system. However, weak analgesics, pure antagonists, and nonnarcotics also demonstrated this effect; and the possible relationship of this effect to the mechanism of action of narcotics was somewhat equivocal.

In the late 1960's and early 1970's Christian and colleagues reported several studies on possible interactions of opiates and cholinesterase. In a study of the binding of a series of N-alkyl substituted normeperidines to butyryl and acetylcholinesterase [1] the importance of hydrophobic binding forces was demonstrated. A correlation of the ED50 (on a modified Eddy hotplate) and the kinetic binding data to acetylcholinesterase indicated a possible similarity in the nature of the analgesic receptor and the active site of the enzyme. Several later studies [2, 3] explored the use of fluorescent dyes to form enzyme-dye complexes to serve as markers to indicate conformational changes of an enzyme after its subsequent interaction with a drug. Although a fully satisfactory marker was not found, further characteristics of the cholinesterases and the fluorescent dye, 1-anilino-8-naphthalene, were described.

Recent Drug Metabolism Studies (1965–75)

Studies in the disposition of morphine were also resumed in the early 1960's. In the continuation of a series of studies initiated elsewhere Mulé studied the distribution of C^{14}-labeled morphine in the CNS of the morphine-tolerant dog following administration of nalorphine [27]. Compared to morphine-tolerant dogs not treated with nalorphine, nalorphine produced a decrease in CNS levels of morphine at 65 minutes, but not at 165 or 275 minutes following C^{14}-morphine administration. Decreases were also seen in morphine levels in heart, lung, liver, and kidney. Plasma levels of free morphine were lower in the nalorphine-treated animals and those of conjugated morphine were initially higher and then the same as in dogs not treated with nalorphine. Since an earlier study had not shown similar interaction effects in the nontolerant dog, the significance of these findings was difficult to interpret. Mulé et al [33] also reported on the intracellular disposition of H^3-morphine in the liver and brain of nontolerant and tolerant guinea pigs, both with and without nalorphine administration. H^3-morphine was found to be primarily localized in the microsomal supernatant fraction and this was not influenced by the state of tolerance or nontolerance or the presence or absence of nalorphine treatment.

Recently, in the present Drug Metabolism and Kinetics Section, the study of the metabolism of morphine has continued, with a reinvestigation of the metabolism of morphine in man by Yeh and his coworkers. In development of a sensitive and specific procedure for separation, identification, and quantitative estimation of morphine and its potential metabolites, thin-layer and gas chromatographic systems were extensively explored. Data have been reported on the potential utility of four TLC development systems and on several GLC systems using trimethylsilyl, acetyl and trifluoroacetyl derivatives [45]. Using these TLC and GLC procedures a study was carried out in four subjects receiving chronic subcutaneous morphine administration, 60 mg four times per day for 4 weeks [47]. Seven consecutive 24-hour urine collections were made from each subject. Free morphine, morphine glucuronide, morphine ethereal sulfate, and, for the first time, free and conjugated normorphine were found as urinary metabolites of morphine. There was indication from glucuronidase hydrolysis experiments that at least some of the normorphine conjugate was a glucuronide; however, the enzymatic hydrolysis was not complete as shown by the greater liberation of normorphine by acid hydrolysis. A subsequent study in dogs [48] showed that in this species normorphine-3-glucuronide was formed. Neither codeine nor norcodeine was identified and it was pointed out that reports by others of the possible formation of these compounds as morphine metabolites could be due to the presence of small amounts of them as contaminants in the administered drugs [46, 49]. Quantitative estimation of morphine and its metabolites was made using both TLC and GLC techniques. A summary of the GLC data is shown in table 1. The values shown for each of the four subjects studied are the mean 24-hour excretions from seven consecutive 24-hour urine collections, expressed as a percentage of the daily administered morphine dose. The grand means showed approximately 8 percent of the administered dose excreted as free morphine, 72 percent as total morphine (that is, free plus conjugate), 0.7 percent as free normorphine and 4 percent as total normorphine. Approximately 76.5 percent of the administered dose was accounted for in the 24-hour urine. TLC estimates were in close agreement with the GLC values.

TABLE 1

Mean 24-hour urinary excretion of morphine and its metabolites in subjects receiving morphine sulfate, 60 mg sub Q q.i.d. Values are expressed as percentages of the daily administered dose. Data from Yeh [47]

Subject	Free morphine	Total morphine	Free normorphine	Total normorphine	Total drug excreted
A	6.60	75.63	0.68	5.19	80.55
B	6.98	60.94	0.51	2.04	62.97
C	9.90	77.11	0.78	6.33	82.80
D	9.63	75.39	0.70	2.49	77.89
Mean	8.27	72.34	0.67	4.15	76.49

Modifications and additions to these GLC techniques have allowed a detailed reexamination of the metabolism of heroin in man [51]. Urine from two clinical studies has been analyzed [50]. In each study 10 nontolerant subjects each received a single intravenous administration of 10 mg/70 kg of heroin. In the first study urine was collected ad lib and every 8 hours for 1 week following drug administration (the samples in this study were also analyzed in a heroin validity study to be described below); in the second study samples were collected for 24 hours, with collection periods ending at 2, 4, 6, 8, 12, and 24 hours. Heroin, 6-acetylmorphine, free and conjugated morphine, and free and conjugated normorphine were identified and quantitatively estimated in the urine. The 24-hour cumulative excretion curve from the second study is shown in figure 1. Heroin and its metabolites were rapidly excreted in the urine. Heroin was identified only in the urine collected in the first 2 hours following drug administration and represented only 0.05 percent of the administered dose. 6-Acetylmorphine, totalling approximately 1.5 percent of the dose, was found for 8 hours; and, total normorphine representing 2.8 percent of the dose was found for 6 hours. Free morphine was found for 12 hours and accounted for about 7 percent of the dose; and conjugated morphine accounted for about one-half the dose in the first 24 hours. Approximately 63 percent of the administered dose was accounted for in the 24-hour urine. Over 96 hours in the first study approximately 80 percent of the administered heroin dose was accounted for, with conjugated morphine representing about 67 percent of the dose. Conjugated morphine was identifiable in a large proportion of urine samples for 3 to 4 days following heroin administration. Urinary excretion half-lives calculated from the second study were approximately 1.3 hours for free morphine and 6-acetylmorphine and 2.7 hours for conjugated morphine and total normorphine.

Studies on the metabolism of narcotic antagonists were initiated in a study of the metabolic disposition of H^3-cyclazocine in the dog, reported

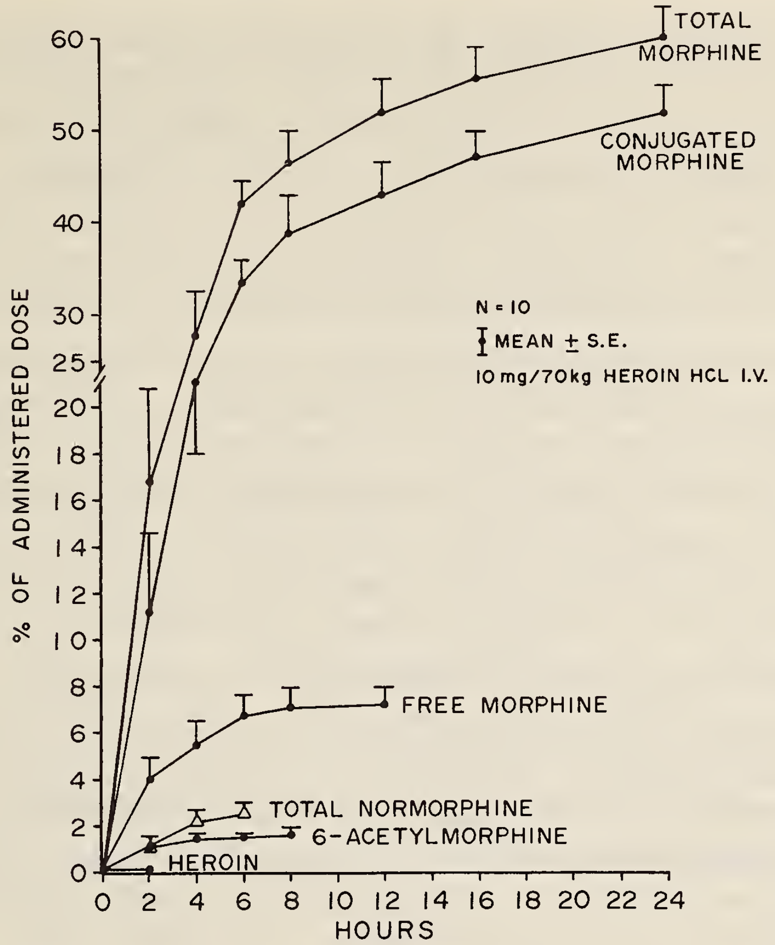

FIGURE 1. *Mean 24-hour excretion curve of heroin and its metabolites following intravenous administration of heroin, 10 mg/70 kg, to 10 subjects. Data from Yeh and Gorodetzky* [50].

by Mulé and Gorodetzky in 1966 [32]. Cyclazocine was administered to nontolerant and cyclazocine-tolerant and abstinent dogs, and urine, feces and plasma were analyzed. Other dogs were sacrificed and drug was determined in different parts of the CNS and other tissues. Free and conjugated cyclazocine were identified as urinary and fecal metabolites. High levels of cyclazocine were found in the CNS of both tolerant and nontolerant dogs, but none was found in the CNS 24 hours after abrupt cyclazocine withdrawal. Little diference was found in the urinary excretion of drug in the nontolerant, tolerant, or abstinent dog, although there was an increase in free cyclazocine in the feces of the tolerant animal. High levels of conjugated cyclazocine were found in the bile. Approximately 40 to 60 percent of the administered drug was not accounted for in the total urinary and fecal excretion over 5 days. An additional 6 to 7 percent of the administered drug was identified in a subsequent study [31] as free and conjugated norcyclazocine, present in the urine and feces. No norcyclazocine was found in the CNS. The conjugates of both cyclazocine and norcyclazocine were identified as glucuronides. Also norcyclazocine was found to have no agonistic effect when tested in the chronic spinal dog. From these studies it was concluded that the higher potency of cyclazocine compared to morphine may be related to its high levels in the CNS, the latency in cyclazocine abstinence did not appear to be related to residual cyclazocine in the CNS, and cyclazocine appears to be markedly metabolized.

Recently studies of the metabolism of narcotic antagonists have been resumed with the study of the metabolism of naltrexone by Dr. Cone and associates in the present Drug Metabolism and Kinetics Section. In 1973, Cone reported [4] the discovery of an unusual naltrexone metabolite in the urine of both subjects receiving single oral 50 mg doses and those receiving the same oral dose chronically once a day. The metabolite described was reduced at the C-6 carbonyl position and analytic and chemical studies revealed that the resultant hydroxyl group was in the beta or isomorphine stereochemical configuration. This is the first time that a metabolite of a morphine-related compound in man has been described with this unusual C-6 isomorphine configuration. When initial attempts to synthesize this compound for use as a chemical standard and for biological testing were unsuccessful, several animal species were explored as possible biosynthetic sources [6]. The dog did not appear to produce this metabolite and results in the rat were equivocal. However, the guinea pig was found to produce significant amounts of both free and conjugated 6 β-hydroxynaltrexone; and urine from chronically naltrexone-treated guinea pigs was pooled and from it several hundred milligrams of the metabolite were isolated and purified in crystalline form. A gas chromatographic analytic method was then developed and a quantitative study of the excretion of naltrexone and its metabolites was undertaken [5]. Six drug-free nontolerant subjects were administered single oral doses of 50 mg of naltrexone and urine was collected at timed intervals for 6 days. Free and glucuronide-conjugated naltrexone and 6 β-hydroxynaltrexone were identified as urinary metabolites. Figure 2 shows the cumulative excretion curve of these metabolites as per cent of

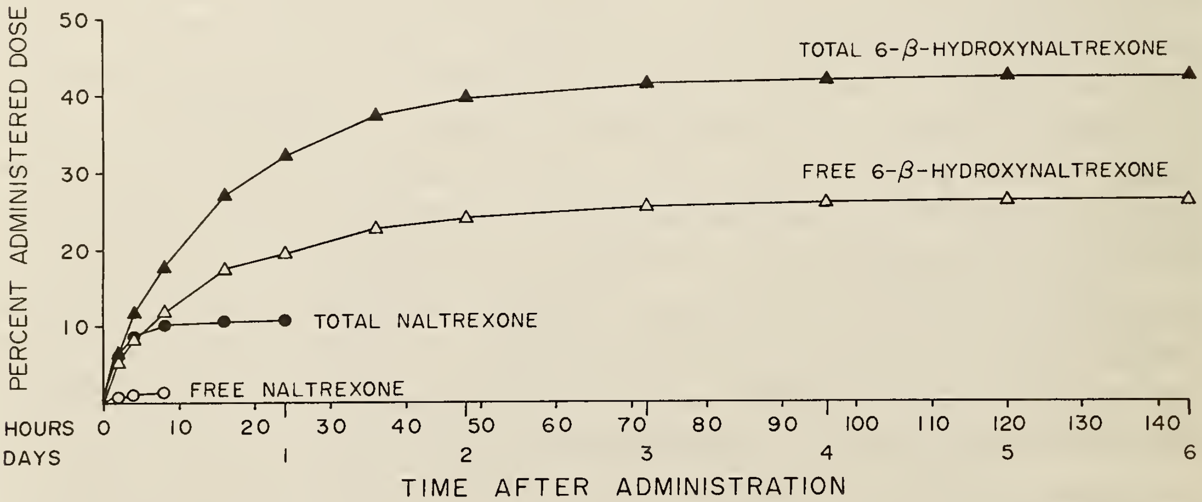

FIGURE 2. *Mean cumulative excretion curve of naltrexone and its metabolites for 6 days following oral administration of a 50-mg dose to 6 subjects. Reproduced from Cone et al.* [5].

the administered dose for 6 days following drug administration. Naltrexone was rapidly metabolized and excreted. Free naltrexone, accounting for 1.2 percent of the administered dose, was gone from the urine of 5 of 6 subjects by 8 hours and in one subject was detectable in the 8- to 16-hour urine. Its mean urinary excretion half-life was 1.1 hours. Conjugated naltrexone represented 9.7 percent of the dose and was detected for 24 hours. Free and conjugated 6 β-hydroxynaltrexone were excreted at a much slower rate and were still detectable after 6 days. The free metabolite was the major excretion product, representing 26.3 percent of the administered dose; it has an excretion half-life of 14 to 18 hours. The conjugated metabolite accounted for 16.4 percent of the dose. The overall recovery of the administered drug was just over 50 percent in the 6-days urine collection. Preliminary studies in the morphine-dependent chronic spinal dog indicated that 6 β-hydroxynaltrexone had weak antagonistic properties and was approximately $^{1}/_{12}$ to $^{1}/_{15}$ as potent as naltrexone. Since the duration of antagonistic effects of this dose of naltrexone is at least 24 hours in man, and free naltrexone is absent from the urine by 8 to 16 hours, it is possible that the 6 β-hydroxy metabolite plays a role in the long duration of action of naltrexone.

Drug Detection Studies: Chemical Tests for the Diagnosis of Drug Abuse (1964–75)

Studies of methods of detection of drugs of abuse in biological fluids primarily for use as screening methods for the diagnosis of drug abuse were initiated by Mulé in the mid 1960's. In 1964 he reported [26] a study of the application of ultraviolet spectrophotometry, thinlayer and gas liquid chromatography to the detection of opiates in the urine. Organic solvent extraction procedures were described and extensive tables of UV, TLC, and GLC data on 31 opioids were reported.

With the establishment of the present Drug Metabolism and Kinetics Section in 1969 we have continued to study chemical tests for the diagnosis of drug abuse, but from a slightly different point of view. It was apparent that with the rapid expansion of drug treatment programs, chemical tests (such as screening urinalysis) would become increasingly important for both the initial diagnosis of drug abuse and for continued monitoring of patients under treatment. However, there was little systematic data available on the validity of commonly used screening methods, that is, on their ability to detect a drug or its metabolites in biological fluids following human drug administration. Validity pertains to answering such questions as: For how long after the intravenous administration of a given dose of heroin can a particular screening method continue to detect morphine in the urine? Such information is of obvious importance to the clinician for the intelligent use and interpretation of urine-screening tests. Our recent studies have been aimed at gathering this kind of information.

However, methodology has not been neglected, especially in our initial studies. Reports have been published by Gorodetzky, and Kullberg and Gorodetzky on methods of extraction of drugs of abuse from urine and on thin-layer chromatography. A method has been described to quantitatively evaluate the sensitivity of TLC as the amount statistically identifiable 99 percent of the time with 95 percent confidence limits on that value; and sensitivity data has been given for 16 opioids, cocaine and quinine [9]. Modifications were described for organic solvent and ion exchange resin impregnated paper extraction of morphine from urine; and standard definitions were proposed for "efficiency of extraction" in terms of the amount of drug reaching the detection system versus the amount in the total urine sample analyzed and for "sensitivity of the overall system" as the drug concentration in urine detectable 99 percent of the time [10]. The organic solvent and ion exchange paper extraction methods presented had 60 and 48 percent efficiencies and sensitivities for detection of morphine (when followed by TLC) were 0.19 and 0.16 μg/ml, respectively. A later paper [24] described studies on the use of XAD–2 resin extraction and showed efficiencies of 63 to 78 percent for extraction of narcotics, sedative-hypnotics and stimulants from urine. The overall sensitivity for detection of morphine in urine was 0.08 μg/ml, more sensitive than the earlier organic solvent and ion exchange paper methods.

Validity studies have been carried out in drug-free nontolerant subjects. Single minimally to highly euphorigenic doses of heroin or morphine have been administered intravenously at weekly intervals in random order to 10 subjects. Urine samples were collected ad lib and every 8 hours for 1 week following each drug administration and then combined into approximately 4- to 8-hour aliquots to provide sufficient volume in each sample to do all the desired chemical tests. The samples were then randomized, coded, and analyzed under blind conditions by well specified and defined commonly used screening methods. Results were reported as the percentage of urine samples positive by 8-hour periods following drug administration. Heroin validity studies have been presented by Gorodetzky et al. [12, 13, 15] and the results are summarized in table 2. OS, IE, and XAD–2 represent extraction of urine by organic solvents, ion exchange resin impregnated paper, and XAD–2 resin both without and with prior acid hydrolysis of urine followed by TLC. TECH is the Technicon Autoanalyzer, a fluorometric technique used without hydrolysis. FRAT is the free radical assay technique. EMIT is the homogeneous enzyme immunoassay technique used with a cutoff

TABLE 2

Validity of common screening methods for detection of morphine in the urine following single intravenous doses of heroin. Each value is the time (by 8-hour periods) for detection of morphine in greater than or equal to 50 percent of urine samples. Data are from Gorodetzky [12], Gorodetzky et al. [13] and Gorodetzky and Kullberg [15]

Screening method[1]	Heroin dose, mg/70 kg, IV		
	2.5	5	10
OS, IE, XAD–2, TECH	0–8	8	16
OSH, IEH, FRAT, EMIT–.5, RIA–200	8–16	16–24	32
XAD–2H, XAD–2RH, EMIT–.3, RIA–100	24–32	32–40	48
RIA–40; RIA–H^3 (50)	32–40	48–56	56

[1] See text for explanation of symbols.

for positives of 0.5 and 0.3 μg/ml. RIA is the I^{125} morphine radioimmunoassay used with cutoffs of 40, 100, and 200 ng/ml. RIA–H^3 is the morphine Abuscreen using a tritiated marker molecule with a 50 ng/ml cutoff. The methods with the shortest time course of detectability were those which detect only free morphine, that is, the three TLC methods and the Technicon Autoanalyzer which use extracts of unhydrolyzed urine. Minimal and moderately euphorogenic doses of heroin were detectable with high probability for only 8 hours following administration and a 10-mg dose was detectable for 16 hours. Hydrolysis of urine prior to organic solvent or ion exchange resin paper extraction or use of the FRAT or EMIT or RIA (with the highest cutoffs) added approximately 8 to 16 hours to the time course of detectability. The XAD–2 resin extraction with hydrolysis (by two methods) was the most sensitive TLC analysis approximately equal in time course of detectability to EMIT with the 0.3 μg/ml cutoff and RIA with the intermediate cutoff. Again, approximately 8 to 16 hours were added to detectability compared to the next less sensitive methods. The longest time course of detectability was seen with the RIA with a 40- or 50-ng/ml cutoff; a moderately to highly euphorogenic dose of heroin was detectable for more than 2 days. A morphine validity study has also been reported [11] in which 6 and 12 mg/70 kg of morphine were administered, equieuphorogenic to 2.5 and 5 mg/70 kg of heroin. Using TLC procedures with organic solvent and ion exchange resin paper extraction, the Technicon Autoanalyzer, FRAT and RIA–H^3, morphine was detectable for about 8 to 24 hours longer than equieuphorogenic doses of heroin.

In addition to gathering validity data on drugs which are commonly abused, we have also been interested in providing information on the detectability of new drugs with significant abuse potential. In a companion study to one conducted by Jasinski et al. on the abuse potential of etorphine, Gorodetzky and Kullberg [16] studied the detectability of this drug in the urine. It was demonstrated that following administration of a highly euphorogenic dose, etorphine was not detectable in any urine sample by commonly used screening methods. Thus, it is unlikely that the abuse of etorphine could be diagnosed by these methods. In a subsequent study [25] using gas chromatography/mass spectrometry, Kullberg showed that less than 1 percent of an administered etorphine dose is excreted as free etorphine in the urine in 24 hours and the concentration in all 8-hour samples was less than 1 ng/ml.

Studies have also been pursued in search of possible new diagnostic applications for chemical tests, and Gorodetzky and Kullberg [14] have reported on the possible use of plasma and saliva for the diagnosis of heroin abuse. Because of the short time course of detectability following single IV doses of heroin these fluids did not appear to be as useful as urine in routine screening for heroin use; however, they may prove useful in the detection of high-dose chronic abuse or in the diagnosis of overdose.

Summary

In summary, interest in studies in biochemical pharmacology and the metabolism and detection of drugs of abuse have fluctuated at the hospital and Addiction Research Center. In the late 1930's and early 1940's the metabolism of heroin and morphine in man were intensively studied. There was then a decrease in research activities in this area for about the next 15 years, although clinical chemical measures were made during several human pharmacologic studies and the metabolism of alcohol was briefly studied. In the early 1960's there was a resurgence of interest with studies of the disposition of morphine and cyclazocine, methods of detecting opiates in urine, and biochemical studies of the interaction of opiates and phospholipids and cholinesterase. This interest was crystallized in the establishment of the present Drug Metabolism and Kinetic Section in 1969 and the continued high level of activity in metabolism studies of morphine, heroin and naltrexone, and in the continuing evaluation and development of chemical tests for the diagnosis of drug abuse.

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Electroencephalographic and Sleep Studies of Psychoactive Drugs

David C. Kay, M.D.

History

Soon after the U.S. Narcotic Farm opened at Lexington (1935), a young psychiatrist by the name of Robert Felix (later, the first director of the National Institute of Mental Health) was assigned to work with addicts there. He became convinced that a then new method of studying brain function, the electroencephalograph, might be important in understanding the effects of addiction on the brain. He persuaded his superiors that the institution should purchase such an instrument, and train someone to use it. So, Dr. Felix was sent to Providence, R.I., to learn EEG techniques and there met Howard Andrews, a biophysicist completing a postgraduate fellowship with Herbert Jasper. After the new electroencephalograph had been independently built and delivered by

Dr. Andrews, Dr. Felix and his superiors agreed that a trained electroencephalographer was also needed to operate their machine. They persuaded Dr. Andrews to come to Kentucky and study addiction with the machine he had constructed. Dr. Andrews' electroencephalograph used storage batteries as a power supply in order to reduce 60-cycle interference, and recorded light signals from 4-string galvanometers on bromide paper strips, so that the amplifier frequency response was not as limited as by the penwriters then available. These bromide paper strips were developed by a photographic process after data collection. Dr. Andrews accomplished several EEG studies before he went to Bethesda in 1943 to participate in atomic energy research. Dr. Andrews' electroencephalograph continued in use at the Addiction Research Center for about 15 years in pioneer studies of the effects of drugs and drug addiction on the EEG. I have been told that this was the first electroencephalograph west of the Alleghenies, and our discussant today (Dr. Andrews) will be able to give us much more of the historical context of his work in Lexington.

As a resident and, later, as a staff psychiatrist, Abraham Wikler learned to operate Dr. Andrews' electroencephalograph, and when he returned from outside training in 1943 he took over Dr. Andrews' laboratory. Dr. Wikler greatly extended the knowledge of drug effects on the EEG with his human studies of opioids, barbiturates, alcohol, hallucinogens, and atropine. He also studied drug effects on the EEG of the cat, rat, and dog, and initiated the use of various instruments, including an 8-channel Grass, Model III, ink-writing electroencephalograph which apparently was acquired from government surplus. In 1963, Dr. Wikler retired from the ARC to expand into another career of teaching and research at the University of Kentucky.

Carl Essig joined the ARC after working in neurological and EEG research with Harold Himwich and Wade Marshall. During his career at the ARC (1954–71) he was involved in the human EEG studies of sedative-hypnotics before turning to his major interest, the mechanism of barbiturate withdrawal convulsions. Dr. Essig initiated the use of portable Grass and Offner electroencephalographs.

Among his many interests in pharmacology, William Martin has had an interest in EEG, and during his time at ARC has fostered the present capability for computer analysis of the EEG. Dr. Martin has studied barbiturate, chlorpromazine, atropine, hallucinogen, and opioid effects on the EEG.

I first came to the ARC in 1964 after psychiatric training to work parttime with Dr. Martin as a MHCD fellow. Dr. Martin and Dr. Wikler encouraged a proposal I made to study the effects of morphine on sleep. This has led to the study of sleep during chronic opioid cycles. During my time at ARC, a Grass model 78 electroencephalograph, instrumentation tape recorders, and a PDP-12 digital computer have been incorporated into the study of EEG and other physiologic measures. We now can analyze several hours of data, which contrasts with the few minutes per sample of bromide paper that were possible in the early investigations.

Drug Effects on the EEG

I. Opioids

As could be expected, several studies have been done at the ARC on the effects of opioids and opioid addiction on the EEG. Single doses of morphine administered to 5 postaddicts (20 mg) or 3 nonaddicts (12–15 mg) showed minimal effects on the EEG [3]. One nonaddict had a "typical sleep pattern" while awake and nauseated; morphine tended to delay the onset of alpha blocking in the postaddicts. A similar effect was shown by single doses of codeine in the EEG of 2 postaddicts [2]. The duration of visual stimulation required to block the occipital alpha rhythm was increased in the one subject who had a dominant alpha pattern. In another study, intravenous injection of morphine produced no obvious EEG effect during the initial orgiastic "thrill", but 9 of 15 EEG records in 10 postaddict subjects then shifted toward synchronization during their subsequent reports of euphoria, relaxation or drowsiness [30]. Single doses of ketobemidone decreased the alpha frequency in 4 of 10 EEG records from 5 postaddict subjects [1]. No EEG effects were seen after administration of single doses of methadone at dose levels below 30 mg, and only one of the 10 postaddict subjects had a shift toward a slower EEG after a 30-mg dose of methadone [18].

Animal studies yielded somewhat comparable results. Sedative doses of morphine (below 20 mg/kg) had little effect on the EEG of 21 unanesthetized rats [7]. Larger doses (20–50 mg/kg) increased the amplitude and decreased the EEG frequency before producing periodic bursts of large 10–12 Hz waves. Although these EEG effects could be interpreted as sedative, the rats had to be restrained because of restlessness. Morphine and methadone had comparable effects on the EEG of 11 dogs [31]. Small doses of methadone (2 mg/kg) or morphine (5–10 mg/kg) produced irregular high voltage slow waves in the presence of EEG fast activity. Large doses of methadone (75 mg/kg) or morphine (200–350 mg/kg) produced seizure discharges of the spike and dome or of the sustained spike pattern; clonic seizures were more prominent after methadone, while morphine produced mostly tonic seizures. Morphine (11–20 mg/kg) decreased amplitude of all EEG activity over the 1–30 Hz frequency range in 4 decerebrate cats [27], and this effect was partially reversed by nalorphine (10 mg/kg).

Several data from these human and animal EEG studies could thus support the concept that subconvulsant doses of opioids are sedative: they decrease the mean EEG alpha frequency in humans, increase EEG slow wave activity and decrease the sensitivity to visual stimulation. In contrast, Kay, Eisenstein, and Jasinski [23] have found that single doses (7.5, 15, 30 mg/kg) of morphine produce a dose-related increase in muscle tension, nocturnal wakefulness, drowsiness and light sleep while decreasing two types of "deep sleep" (delta sleep and REM sleep). This sleep study in 8 human postaddicts demonstrates a stimulant effect of morphine which parallels the time course of behavioral stimulation commonly produced in postaddicts by opioids.

Chronic effects of opioids upon the EEG have been studied more intensively. Andrews [3] found that the alpha index was increased in 50 addicts (stabilized on morphine) when compared to published data on 401 controls. In contrast, 50 individuals who had been withdrawn from opiates for at least 1 year (postaddicts) tended to have either a very low or a very high alpha index. During acute withdrawal of morphine the occipital alpha activity was not decreased in any subject observed. Such a decrease in alpha index required several days after withdrawal of drug before becoming manifest. The alpha frequency tended to be higher in the postaddict population, and slower EEG activity (less than 7 Hz) was greatly reduced following withdrawal in those individuals who had shown slow EEG activity during addiction. In a study of 2 postaddict subjects through a complete cycle of physical dependence, Andrews [5] found a decrease in both alpha frequency and alpha index during times when the morphine intake was increased; this was seen in the one subject who had a dominant alpha pattern prior to addiction. Partial tolerance developed to these effects during chronic drug intake and both alpha index and alpha frequency were returned to control level 30 days after withdrawal of morphine. During chronic morphine administration the slow EEG frequencies were present during alert behavioral states, and these slow patterns could be temporarily replaced by alpha activity during visual stimulation with a light. In Andrews' other test subject, who had no sustained alpha activity during initial control, alpha activity appeared only after the dose of morphine was rapidly increased to more than 300 mg daily. This alpha activity was gone 30 days after withdrawal of morphine.

Kay [22] described the effects on sleep of chronic administration of morphine (140–240 mg daily) to 6 subjects: in comparison with the predrug control, delta sleep (early night) shifts toward later in the night, waking state is increased during the middle of the night, and REM sleep (late night) is decreased. Although these effects would indicate a persistent arousal by chronic morphine, such an arousal is much less than that produced by single doses of morphine in nontolerant subjects [23].

Other opioids do not produce exactly the same EEG pattern as does morphine. The alpha index was increased by administration of the stabilizing dose of morphine in 7 subjects maintained on chronic morphine [2]. The same subjects showed a lower preinjection alpha index after substitution of chronic codeine for the chronic morphine, with a greater postinjection increase by doses of codeine; the peak alpha index after the stabilizing dose of codeine was comparable to that after morphine. The changes in alpha frequency were inverted but somewhat similar: the stabilizing dose of each drug decreased the alpha frequency; the alpha frequency after the codeine dose was higher than the frequency before the morphine dose. Chronic administration of codeine increased the differences in EEG between hemispheres, with greater alpha index and lower alpha frequency being seen in the right hemisphere. High alpha index was also seen during acute withdrawal from codeine at a time when there was behavioral agitation. Andrews [6] studied the effect of substituting several derivatives of morphine in subjects dependent on morphine. Alpha-isomorphine, codeine, and isocodeine decreased alpha index by general reduction of rhythmic activity; dihydromorphine and methyldihydromorphinone decreased alpha index by increasing beta (above 16 Hz) or "delta" (below 7 Hz) activity, with some EEG delta activity emerging during withdrawal; heroin, dihydrodesoxy-morphine, and dihydroalpha-isomorphine produced no obvious change when substituted for morphine. Meperidine showed much more dramatic EEG effects during chronic intoxication [4]. Slow waves appeared in the EEG of 5 subjects after a few days of increasing dosage, and the EEG showed a progressive decrease in frequency and increase in amplitude as the subjects spontaneously increased drug dosage. The subjects also demonstrated tremor, nervousness and muscle jerking; some experienced episodes of unconsciousness, tongue-biting and hallucinations. The EEG slow waves persisted for up to 48 hours after withdrawal of meperidine. Comparable EEG effects were seen with chronic administration of ketobemidone [1]: Delta index (less than 7 Hz) was increased in 5 subjects, with an accompanying broadening of power in the EEG frequency spectrum of 3 subjects; tolerance developed to these effects. In 2 subjects who had intermittent slow EEG activity during predrug control there developed paroxysmal high voltage slow activity, as well as one occasion of spike and dome EEG pattern, during addiction to ketobemidone. Slow wave activity was increased in all 5 subjects during acute withdrawal, but no clinical seizures were observed either during chronic drug administration or after withdrawal. EEG records became normal by 3 days after withdrawal of ketobemidone.

Chronic administration of methadone produced somewhat different results [20]: A progressive shift toward slower EEG frequencies was seen during chronic methadone in 14 subjects. In the subjects with a dominant alpha pattern during predrug control, both the alpha index and the alpha frequency were decreased during chronic methadone, while theta activity (4–7 Hz "delta") was increased. The threshold dosage for such EEG slowing varied from 20 mg to 180 mg daily; partial tolerance to this EEG slowing was seen in 10 of the 14 subjects. EEG slowing persisted for 2 to 5 days after drug withdrawal. Such EEG slowing by chronic methadone has been confirmed in 6 subjects at a 100 mg daily dosage [28, 21]. Delta (1–3 Hz) and theta (4–7 Hz) activity were increased during drug administration, with a slowing of the dominant alpha (8–12 Hz) activity and a decrease in beta (15–30 Hz) activity. Although subjects reported an increase in daytime sleep during chronic methadone, little obvious change was apparent in their quantified nocturnal sleep. A small but significant increase in bursts of delta activity (4–20 sec in duration) has been seen in the sleep of subjects receiving chronic morphine [22] or chronic methadone [21]. During early abstinence (6 weeks after withdrawal of methadone), delta and theta activity were greatly reduced in the daytime EEG, while beta activity was increased and the mean EEG frequency was increased. Alpha index was decreased and beta index increased during protracted abstinence (10–22 weeks). Sleep was grossly disturbed for 3 to 5 weeks after withdrawal of methadone. Quantified study then found an increase in sleep 6 to 22 weeks after withdrawal, with an increase in both REM sleep and delta sleep during protracted abstinence (10–22 weeks).

II. Barbiturates

Although limited in number, ARC studies on the EEG effects of barbiturates have been of value in the pharmacology of barbiturates. Martin and Eades [26] assessed the interaction of pentobarbital (4, 8, 12 mg/kg) with midbrain stimulation (2.5–5.0 volts) in the production of EEG spectral patterns. This study in 7 cats, immobilized with succinylcholine, utilized an Offner electroencephalograph and an Offner frequency analyzer to quantify the EEG. Pentobarbital produced a dose-related increase in amount of spectral activity (amplitude of EEG) with a peak in the 4–14 Hz range. All doses increased spectral activity by about the same amount in the 16–30 Hz range, but there was a dose-related increase by pentobarbital in the 1.5–12.0 Hz range. This pattern resembles that of the cerveau isolé preparation more than that of the encéphale isolé preparation and differs considerably from that produced by atropine. Midbrain stimulation in cats after administration of pentobarbital produced a shift of the peak spectral activity to faster frequencies. This increase in frequency was directly proportional to the strength of stimulus, and inversely proportional to dose of pentobarbital. Pentobarbital also progressively increased the threshold of the activating responses. In another study single doses of pentobarbital (75, 150 or 300 mg/70 kg) when administered to 8 men produced a dose-related increase in spindle burst incidence and spindle (stage 2) sleep, as well as a decrease in REM sleep and minimal effects on delta sleep [24].

EEG measurement was part of the three classic ARC studies on experimental barbiturate addiction: Isbell et al. [17] found that chronic intoxication with barbiturate (1.3–3.8 gm daily) in 5 men (previously abstinent from all drugs for at least 3 months) produced an increased amplitude of all frequencies of the EEG, especially "delta" waves (1–6 Hz): tolerance developed to the increase in "delta" after 1 month, while beta (15–30 Hz) activity became greatly increased and the general increase in EEG amplitude persisted. During the first 12 to 48 hours after abrupt withdrawal of barbiturate, paroxysmal bursts of high amplitude slow (4–6 Hz) waves appeared in the EEG of all 5 subjects; this EEG sign preceded the grand mal seizures of the 4 subjects who convulsed. An EEG recorded during the clonic phase of a convulsion showed bursts of high amplitude 30–50 Hz spikes, with "stupor" waves (1–6 Hz) afterward. Increased 6–7 Hz EEG activity was seen for 2 weeks after drug withdrawal, but by 1 month after withdrawal EEG's had returned to control levels.

Fraser et al. [14] and Wikler et al. [32] studied secobarbital in two groups of subjects: 14 men at maximum intoxication possible (900–2,600 mg daily) and 21 at moderate intoxication (600–800 mg daily). During maximum intoxication, the EEG showed mixtures of fast and slow abnormalities, mainly in the frontal and parietal tracings, with no tolerance demonstrated for these effects. Upon withdrawal, 11 men convulsed, and marked EEG changes appeared, generally having periodic hypersynchronization, with frequent mixed spike and slow wave or spike and dome (4 Hz) paroxysmal discharges. Only mild EEG abnormalities lasted longer than 8 days after withdrawal. During moderate intoxication, EEG tracings showed predominantly rhythmic fast activity in the frontal and parietal leads. Upon withdrawal, random slow activity was present in half the EEG tracings, with 37 percent having paroxysmal records in the 2d or 3d day of abstinence; only 2 of these subjects had clinical seizures. Random slow activity persisted in about half the EEG tracings later than 8 days after withdrawal.

Essig and Fraser [12] and Fraser et al. [15] studied a 400 mg daily dosage of pentobarbital (8 subjects) or secobarbital (10 subjects). During chronic intoxication sleep was observed to be increased for only 30 days. The EEG showed an increased amplitude of rhythmic 18–30 Hz (beta) waves in frontal and parietal areas during chronic intoxication. A general increase in EEG amplitude was also seen during the first week of intoxication, with a reduction of alpha in 3 of 6 subjects. Some tolerance developed to the production of EEG fast activity in 7 of 13 subjects, but this was least in the frontal leads. During withdrawal no seizures were observed, but 5 of 18 subjects developed paroxysmal EEG discharges.

Barbiturate-withdrawal convulsions have been investigated by Essig [10]. These convulsions do not absolutely require cerebral or cerebellar cortex, although some decorticated dogs develop sham rage attacks instead of convulsions [8]. Chlorpromazine or diphenylhydantoin do not antagonize such seizures [11, 13], but amino-oxyacetic acid does [9].

III. Alcohol

EEG aspects of alcohol intoxication and the alcohol abstinence syndrome have been investigated in two studies at the ARC. Isbell et al. [19] and Fraser et al. [33] found in 3 subjects that initial intoxication with alcohol was associated with diffuse slowing of the EEG; partial tolerance developed to this effect. Upon withdrawal, transient spikes, sharp waves or rhythmic paroxysmal discharges were seen in the EEG in the 15–19th hours of abstinence. With increasing severity of abstinence, occipital alpha was decreased. One subject had a convulsion at the 41st hour of abstinence. Because the barbiturate and alcohol intoxication and abstinence syndromes have many similarities, Fraser et al. [16] examined the equivalence of chronic alcohol and chronic barbiturate intoxication in 10 men. They found that substitution of alcohol for barbiturate caused the EEG to shift from a dominant fast activity pattern to a diffuse slow activity pattern. EEG changes were not seen upon withdrawal of alcohol but 7 of the 10 men did not have their EEG sampled in the 16th–33d hours, when such EEG changes might be expected.

IV. Hallucinogens

Williams et al. [34] found that single doses (30 mg or 120 mg) of pyrahexyl compound had little effect on the EEG of 4 men, while chronic pyrahexyl compound intake produced marked EEG slowing in 5 men. Normal EEG tracings were seen on the 4th day after withdrawal of pyrahexyl compound. These authors also studied the EEG effects of marihuana: smoking 1–4 marihuana cigarettes produced no obvious change in the alpha frequency of 18 subjects, but muscle activity increased greatly, and alpha index tended to decrease. These effects disappeared during chronic marihuana smoking (9–17 daily cigarettes for 7–36 days). Wikler [30] studied the effects of a single dose of mescaline (5–10 mg/kg) in 11 postaddicts. The EEG's showed either "no change, intermittent or continuous replacement of alpha activity by low-voltage fast activity and/or increase in frequency of the alpha rhythms." Comparable EEG effects were also seen after 15–75 mg of nalorphine, with some occasional random or rhythmic slow EEG activity.

V. Chlorpromazine

Martin et al. [25] found that chlorpromazine (1–10 mg/kg), chlorpromazine sulfoxide (5–20 mg/kg), and three other phenothiazines all produced EEG slow-wave activity in the succinylcholine immobilized cat: bursts of 8–12 Hz waves, bursts of 2–4 Hz high amplitude waves, and increased 6–8 Hz activity. These compounds also depressed activation of the EEG, and generally enhanced cortical-evoked potentials. Martin and Eades [26] found that chlorpromazine (1–10 mg/kg) and chlorpromazine sulfoxide (5–25 mg/kg) both produced EEG slow waves in the cat with maximum activity in the delta (1.5–3.5) range of the frequency spectrum, which resembles the frequency spectrum of the encéphale isolé cat. Moderate strength of stimulation of the reticular formation produces both an enhancement of 8–16 Hz activity and a decrease of delta activity in cats receiving chlorpromazine; higher stimulus strength abolished both delta and higher frequency peaks. The authors concluded that the depression of the excitability of the ascending activating system by these drugs appears to be better correlated with their adrenergic potentiation rather than with their adrenergic blocking activity.

VI. Atropine

Wikler [29] described a "sleep pattern" in the EEG of 12 dogs after 2–8 mg/kg of atropine: alternate bursts of 8–12 Hz rhythmic discharges and random or rhythmic high-voltage 2–6 Hz waves. However, the dogs behaviorally alternated between "excitement" and sedation. Such a burst-slow wave EEG pattern can also be produced by pentobarbital (15 mg/kg), and nalorphine (2.5–30 mg/kg), with greatly differing behavioral states. Martin and Eades [26] found in 7 succinylcholine immobilized cats that atropine sulfate (0.2–5.0 mg/kg) produced EEG slow activity with a peak at 1.5 Hz, and little effect at frequencies above 16 Hz. Increasing activation of the EEG by midbrain stimulation reduced this delta activity. The EEG effect of atropine is therefore of a different pattern than that of pentobarbital.

Conceptual Development

After Felix had the idea of investigating addiction by means of the EEG, Andrews attacked the problem by using two designs developed by Himmelsbach: the chronic opiate cycle (predrug control, chronic drug intake, and postdrug withdrawal), and substitution of drugs for chronic morphine. Andrews described two phenomena which appear to be worth further investigation: (1) An increase in EEG alpha activity during chronic morphine, which persists even during acute withdrawal, and (2) a differentiation of postaddicts into groups with either very high or very low EEG alpha activity. Andrews also investigated a variety of opioids and found that they did not all have the same pattern of effect on the EEG, with some (e.g., meperidine) showing EEG evidence of convulsant activity. Wikler confirmed such EEG convulsant patterns for opioids in man and animals.

Wikler sought to correlate EEG patterns with behavior patterns, and clearly described the dissociation of EEG "sedation" (slow wave) patterns from the behavioral effects of barbiturate, morphine, nalorphine, and atropine. He later described a tendency for EEG synchronization to be correlated with pleasurable states, and EEG desynchronization with anxious states, when comparing the effects of morphine and two psychotomimetic drugs (mescaline, nalorphine). Both the concept of EEG/behavioral dissociation and the concept of EEG synchronization correlated with pleasure have stimulated the field of EEG research. In describing the EEG convulsant patterns during withdrawal from barbiturates and alcohol, Wikler used these phenomena to support the concept that barbiturates produce physical dependence, with the EEG as a sensitive measure of this dependence. Essig then investigated the phenomenon of barbiturate withdrawal convulsions, and accumulated indirect evidence that they might be mediated by GABA depletion, probably in the brain stem. In investigating the interaction of drug effects and midbrain stimulation, Martin has demonstrated the value of quantification of the EEG, with differentiation of barbiturate effects from atropine effects. Kay initiated studies of opiate effects on sleep and has described an arousal effect by morphine which might be related to morphine-induced euphoria.

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Comments on Electroencephalographic and Sleep Studies

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In 1936, Dr. Robert Felix proposed that the techniques of electroencephalography, just being developed, be applied to the problems of drug addiction. This proposal was greeted with enthusiasm by the small group then working in the field. It seemed almost inevitable that a drug such as morphine which produced such a marked change in the user's reaction to his environment, and which could lead to addiction with physical dependence, must have a profound effect upon the cerebral cortex and upon the electrical potentials recorded therefrom.

In due course the program proposed by Dr. Felix was implemented and was pursued vigorously at the Lexington Hospital. It was my privilege to participate in the program almost from its inception. When I left the program in 1942 it was with a distinct sense of disappointment and personal failure. Some interesting observations had been made and studies made during a complete cycle of readdiction and withdrawal had demonstrated some self-consistent changes in the electroencephalograms of two subjects. However, no conclusions of basic significance of these observations toward a better understanding of the mechanisms behind drug action, tolerance development, or the withdrawal syndrome were drawn. From the vantage point of 1975 it appears that this lack of definitive results can at least partially be assessed against the technique itself and not entirely against those who were applying it to the problem at hand.

It now seems clear that the recognizable information content of an electroencephalogram is considerably less than the earlier enthusiasts had hoped. Essentially nonrepetitive, an electroencephalogram consists of one, or perhaps a combination of two dominant frequencies, each with nonsinusoidal waveforms. A dominant frequency has only two degrees of freedom when it is disturbed by some external agent such as drug administration; the frequency can either increase or decrease. Similarly the degree of dominance, which is to say the fraction of the time that a given frequency is present, can also only increase or decrease. This state of affairs contrasts sharply with the information content of an electrocardiogram, where the repetitive patterns permit drawing very basic conclusions about the state of the single generating source, the heart.

In the late 1930's Loomis and his collaborators were doing important pioneer work in studying the electroencephalogram during sleep. In spite of some ingenious experimental arrangements, record reading was a tedious, time-consuming business fraught with uncertainties and personal evaluations. Record taking and record reading were related on a time scale not unrelated to that described by the Queen of Spain "nine minutes pleasure and nine months pain."

Today the phenomental developments in electronics have changed the situation drastically. Modern analytic techniques can be used to derive meaningful, quantitative values from the long records taken during full sleep cycles. Some new techniques have yet to be applied to the recording of brain potentials. Detailed frequency analyses, where the nonsinusoidal wave forms are forced into an equivalent series of harmonic frequencies, have not been particularly helpful. Perhaps the methods of lock-in amplification, now in common use for extracting information buried in background noise can be applied to separate repetitive from random fluctuations in the electroencephalogram.

Many years ago d.c. amplifiers were discarded for use in routine electroencephalography because the difficulties involved in obtaining a stable recording system were out of proportion to the additional information obtained. Today the problems of stability can be more easily dealt with, and d.c. amplifiers, routinely used, might yield some data currently being missed.

In addition to considering the use of new recording and data-handling techniques thought should be given to attempting to influence the encephalogram and possibly human behavior by externally applied electric currents or magnetic fields. Mayer and Hayes [1] have recently reported that in the rat tolerance to electrically induced analgesia develops, and that this is cross-tolerant to morphine. Conversely addiction to morphine greatly reduces the degree of analgesia producible with electric currents. Perhaps electric currents applied through properly placed electrodes will be found to influence the human brain and the electroencephalogram in a manner similar to the influence of addicting drugs.

It seems that 1975 could be another exciting year. Techniques are now available for a more sophisticated attack upon the drug addiction problem through the study of cortical potentials. New and more powerful methods of data analysis are at hand. Perhaps no new basic information will be forthcoming from a new attack. This is the gamble inherent in any research project, and here the gamble seems well worth taking.

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Historical View of the Characteristics of Addicts

In Isbell's[53] historical review of addiction, two broad conceptions of addicts were differentiated: one that he is a sick person and the other, that he is a dangerous criminal. The connection of addiction with vice or criminality was related to importation of Chinese laborers who smoked opium and the spread of this practice to psychopathic types.

Kolb [58] who was assigned to the study of drug addiction in 1923 by the United States Public Health Service soon emphasized the importance of psychopathic characteristics in addicts and the relevance of these for both starting and relapsing to narcotics and for susceptibility to its euphoric effects. According to Pescor [79] the psychopathic type was likely to relapse, but other factors were also predictive. Kolb [58] regarded some nonpsychopathic factors such as memories and associations connected with opiate drug taking such as pain before getting the drug, worry about getting the drug, and relief after obtaining a shot, as important for relapse. Wikler [91] emphasized relief from abstinence as important for relapse.

Kolb developed a typology which was regarded as useful for classification purposes by Pescor [78] and Felix [18]. The categories were: (1) normal, (2) psychopathic diathesis, (3) psychoneurotic, (4) psychopathic personalities, (5) inebriate personalities, and (6) addicts with psychoses. According to Felix [18] morphine serves different purposes in different subtypes. The psychoneurotic used opiates to relieve his symptoms; whereas, the psychopath used drugs as an aggressive act of daring or as a way to obtain pleasure. In Kolb's terms, using drugs to obtain relief from symptoms is negative pleasure and is psychoneurotic, and using drugs to arise above one's plane is positive pleasure and is psychopathic. These two functions of the drug have continued to be dealt with by Wikler and Rasor [92] and Monroe and Hill [71]. Both of these rationales for drug use represent an approach. An avoidance aspect can also be distinguished in which a subject emphasizes damage from a drug [39].

Measurement of Personality Characteristics of Opiate Addicts With Psychological Tests

Personality tests given before 1950 were not indicative of distinct characteristics of opiate addicts or types among this group. In the Braucht et al. [9] review only one reference to a Vogel, Isbell, and Chapman paper was dated before 1950. The Rorshach test, which was frequently used before that time, has never been regarded as particularly valid for identifying psychopaths, but young addicts did differ from their controls [22]. Brown [10] found that such tests as the Bernreuter or Neymann-Kohlstedt Schedule of Introversion-Extroversion were ineffective for showing differences between addicts and normal subjects. As rated by a variety of tests given in the 1930's addicts were below average in intelligence [80]. Later, Brown and Partington [11] found that addicts had average intelligence and were within the average range on subscales on the Wechsler Intelligence Test. Wechsler [89] claimed that psychopaths do better on the performance rather than on the verbal portion of his I.Q. test. Most investigators consider intelligence unimportant in the psychopath, but Lindesmith [60] thought that some minimal level of intelligence was required for an addict to conceptualize the utility of opiates to treat his withdrawal symptoms. Most addicts show some intellectual impairment on the Shipley test [49], but this is not the case with physician addicts. Partington [77] found that addicts were lower on learning and motor abilities.

The psychopath has been regarded as deficient in capacity to learn or to profit from learning, especially in social learning [42]. The psychopathic addict who is free of anxiety is responsive to immediate reinforcement in learning experiments as compared to those who have an abundance of anxiety [15, 76], but the anxious psychopath is most similar to the normal subject in the response to more remote reinforcement [76]. The more maladjusted addict [5] is more susceptible to pressures from addicts than professionals. Learning related to drugs occurring in addicts is affected by factors other than psychopathy. Associations to methadone increase as a function of experimental addiction to methadone [34]. Opiate addicts who are primarily heroin addicts gave more associations to heroin than to any other drug [33, 34].The street addict, who has presumably been exposed to an addict subculture, gave more drug argot associations in a free association test than did criminals, medical addicts, or normals [62]. Addicts perceive drug argot related words more quickly than normals [56]. Vocalization of drug argot words has an impact on pupillary response; pupil dilation is regarded as an indicator of emotional responsiveness and as an indirect indicator of commitment to drugs under this experimental circumstance [4]. Pupillary diameter increased in response to argot words and this increase was correlated with scores on a Language-of-Addiction scale for opiates.

The development of the MMPI [43] and such scales as the Psychopathic Deviate scale encouraged a tremendous number of diagnostic studies up to 1960 [14]. Since that time studies on drug abusers have been increasing rapidly up to the present time. In a large variety of institutions, high psychopathic traits have been found in opiate addicts as measured by the MMPI whether the subjects were young or old, Negro or white, male or female, prisoners, probationers, volunteers, or NARA patients, on or off methadone, etc. [3, 6, 8, 12, 16, 20, 23, 29, 31, 32, 44, 46, 47, 49, 69, 72, 74, 82, 83, 84, 85, 87, 88, 90].

In the first classificatory study of opiate addicts at the Public Health Service Hospital at Lexington by Hill, Haertzen, and Glaser [47] using the MMPI both volunteers and prisoners were tested when they were free of opiate-withdrawal symptoms. Subjects were classified according to their score elevation and their two highest scores among the clinical scales. One type was defined as normal and three other types were considered to be character disorders. Five and one-half percent obtained profiles within the normal range; this percentage was considered to be in agreement with that found in the prior study of Pescor [78] done in the 1930's. A so-called psychopathic type was characterized by having the highest and second highest score on the Psychopathic Deviate or Mania scale; 30.5 percent fell in this class. These subjects were presumed to be similar to those defined by Kolb as being the least likely to complain of withdrawal symptoms. Neurotic (19 percent) and schizoid types (17 percent) were also distinguishable, but the Psychopathic Deviate score was also very high in both of these subtypes. This led Hill, et al. [47] to emphasize initially the pervasiveness of psychopathic characteristics among opiate addicts. Such characteristics appeared equally common to committed alcoholics and criminals [46]. This is not to say that other characteristics are without import as each type identified by a typological analysis is somewhat unique in its predictive value [6, 46]. To illustrate, Gerard and Kornetsky [21] thought that schizoid types were frequent among young addicts in fringe areas where drug use is accepted, and that such types are at a relatively greater risk to continue the use of drugs to addiction (see Hill, et al. [47], p. 137).

In more recent studies by other investigators [9, 44, 51] including those at the Clinical Research Center [6, 69] there has been some tendency to emphasize the importance of the different personality types found in samples of drug abusers and to deemphasize psychopathy. This deemphasis, for example, is based on differences between addicts identified as volunteers, civilly committed patients (NARA), prisoners, and probationers and the differential distribution of subtypes within these groups. Characterological disorders (highest Psychopathic Deviate or Mania score) were most frequent in prisoners and probationers and least in the NARA's. Emotional disturbances, that is, frequent neurotic types, were highest in the volunteers who frequently needed to be withdrawn from opiates [69].

In a cluster analysis of these four groups, Depression, Psychopathic Deviate, and Schizophrenia scales were elevated for the first factor and in the second factor the Psychopathic Deviate scale was high relative to all other scales [6]. The second factor, as found in males, was more like the first factor determined earlier in a study of addicts, alcoholics, and criminals [46]. The two identified subgroups did not differ significantly on the Psychopathic Deviate scale.

As indicated by the above discussion, drug abusers do differ and many of these differences are greater than those found between addict prisoners, committed alcoholics, and criminals [46]. It should be noted that in all addict samples the Psychopathic Deviate scale is elevated. The averages obtained for the different types of samples may constitute useful standard models for classification of addicts. Table 1 shows the average T-scores of types of samples which do differ. These are:

1. Prisoner opiate addicts who volunteered for research studies with drugs [27, 36]. In this group, the Psychopathic Deviate and Mania scores are high relative to those on other scales. They also scored higher on an Antisocial scale [31] and a Severity of Opiate Addiction scale [39].

TABLE 1

MMPI Average T-Scores of Drug Abuser Types

	Scale	Research Addict[1]	Detoxification[2]	Physician Addict[3]	Multidrug Abuser[4]
L	Lie	50	49.82	51	44.78
F	Faking bad	59	69.04	51	77.07
K	Defensiveness	55	51.34	59	48.76
Hs	Hypochondriasis	53	68.05	58	60.55
D	Depression	60	74.30	61	74.25
Hy	Hysteria	54	66.64	62	66.89
Pd	Psychopathic deviate	73	78.96	65	82.65
MF	Masculinity-Femininity	59	61.35	63	73.79
Pa	Paranoia	54	65.32	58	68.56
Pt	Psychasthenia	57	69.55	57	76.93
Sc	Schizophrenia	60	73.25	52	88.15
Ma	Hypomania	68	69.78	56	72.59
Si	Social introversion	50	55.25	47	61.37

[1] Prisoner-addicts who volunteered for drug research studies [27, 36].

[2] Opiate addicts who elected to take detoxification or therapy without opiate maintenance: males and females electing opiate detoxification at the Haight-Ashbury Clinic [82], opiate addict volunteers at the Clinical Research Center [8], and addicts treated under NARA at the Tulane Medical School Department [87].

[3] Addict physicians who were predominantly volunteers and addicted to Demerol [49].

[4] Samples are made up of subjects who have used many drugs but not opiates: Hospitalized adolescent drug users from the Langley-Porter Neuropsychiatric Institute in the Youth Drug Study Unit (YDSU) and its companion sample of nonhospitalized drug users from a counseling program for teenagers in West Los Angeles called Developing Adolescents Without Narcotics (DAWN) [12], drug abusers of marihuana, amphetamines, psychedelics, and barbiturates in Encounter [44], and young males treated at the Drug Abuse Clinic of the Texas Research Institute who had predominantly used marihuana, amphetamines, and a variety of barbiturates [84].

2. Opiate addicts who have elected detoxification or a therapy which does not involve maintenance with methadone [8, 82, 87]. These subjects show a relatively greater amount of depression and diffuse symptomatology, including psychopathy.
3. Volunteer physician addicts who generally have been addicted to Demerol [49]. These subjects had an elevation on the Psychopathic scale but they are the least psychopathic and have many defenses against showing symptoms.
4. Multi-drug users who have generally not used opiates at all or only infrequently [12, 44, 84]. These subjects obtained an extremely high score on the Schizophrenia scale and showed other symptoms indicating a thinking disorder; they practically showed no resistance to revealing psychological disturbances. This group has the highest score on the Psychopathic Deviate scale.

Other personality tests show characteristics of opiate addicts or drug users. Thus, opiate addicts volunteering for drug research at the Addiction Research Center [27], as well as other types such as frequent marihuana users [51], and psychedelic drug abusers [57] scored low on the California Psychological Inventory scales of Responsibility and Socialization which measure psychopathic characteristics, but opiate addicts did not differ from alcoholics on a Retreatism scale [73]. Opiate addicts were rated as emotionally unstable (C scale), suspecting and jealous (L), eccentric and unconcerned (M), insecure and anxious (O) in several studies on the 16 P.F. [35, 81].

Addicts and normals differed in their relative ranking of risky and cautious values [68]. Addicts placed greater value on their own life; whereas, normals valued the life of their husband/wife. Addicts valued avoiding risk of failure in a career; normals valued making a useful contribution to the health and welfare of society.

On the Addiction Research Center Inventory, narcotic addicts relative to other clinical groups obtained the highest score on the Psychopath scale [27, 41]. These were followed by criminals and alcoholics. Mentally ill and normals obtained the lowest scores. On the Maladjustment scale, the four clinical groups were higher than normals. On the Social Withdrawal scale the mentally ill were high; whereas, the other four groups were low.

One of the most frequently expressed ideas about opiate addicts is that they will abuse opiates as well as other drugs: amphetamines, barbiturates, alcohol, etc. This leads to the notion that any scale purporting to measure characteristics of abusers of any one of these types of drugs will also function as a general discriminator for abusers and nonabusers of drugs. Thus, it would have been quite within the range of acceptance if addicts scored highly on any of the many scales which stress the impact of alcohol on one's life such as the Manson Alcadd [63]. However, opiate addicts were within the normal range on the Alcadd [31] and on the Alcoholic Language of Addiction Scale of the Inventory of Habits and Attitudes [39, 40]. In a drug-oriented matched form of this alcoholic test called the Hill-Monroe Personal Inventory [71], opiate addicts obtained a high score and alcoholics and normals obtained a low score [70]. In reference to the scale content, addicts say they use drugs, but not alcohol, to ease their discomfort. Alcoholics, on the other hand, respond in the opposite way on drug and alcohol labeled items in the Language of Addiction Scale. That is, they would use alcohol to ease their discomfort but not drugs or opiates [70].

Staying in Treatment

Painting [75] could not distinguish between volunteers who did or did not leave the U.S. Public Health Service Hospital against medical advice (AMA) with the MMPI but in a later study by Levine and Monroe [59], a distinction was possible when control was made over legal pressure. In another study of volunteers in treatment, subjects showing the greatest subjective opiate-withdrawal symptoms after 10 days (time when treatment for withdrawal was ended) were most apt to leave AMA [67].

Staying in NARA Aftercare Programs and Successful Completion of Probation

A significant interaction was found between the category of supervision classified as NARA aftercare vs. probation and success of treatment dichotomized into success vs. failure with several scales of the MMPI and Personal Inventory [17]. Thus, successes in NARA showed a greater Acceptability for Psychotherapy or Middle Class Standards and less Severity of Opiate Addiction; whereas, successful probationers had the opposite characteristics. Success was more predictable in the probationer.

Selection for Psychotherapy

Perhaps the most predictable characteristic using psychological tests in opiate addicts is their acceptability for psychotherapy [71]. Professionals from a variety of mental health disciplines agreed on who would be acceptable for psychotherapy [66]. An Acceptability for Psychotherapy Scale [71] developed in the McLean et al. study [66] on volunteers and prisoners is still predictive of which subjects will be regarded as acceptable [7].

Subjective Drug Effects

Acute Drug Effects

Personality or psychopathology tests such as the MMPI and the Guilford-Zimmerman Temperament Survey which measure enduring or stable characteristics have not been very useful for showing acute drug effects [27, 29, 38]. Exceptions have been found as for LSD [3]. On the other hand, mood tests or tests which stress immediate or current experience have been widely and successfully used for the measurement of drug effects. Mood adjective check lists may be very short and still be quite effective for showing change [2, 13, 19, 54, 55, 61, 64].

In the development of the Addiction Research Center Inventory [45] an attempt was made to bridge the gap between the measurement of psychopathology, personality, and subjective drug effects or experiences by the broad sampling of questions, controlling of the format of questions [30], and then developing scales which would measure differences between drugs, clinical groups, or personality types [24, 25, 27, 28, 41, 48].

Typically, more than one drug scale for a given drug has been constructed. An empirical scale is made by selecting items which differentiate a drug in question from placebo, the universal standard, to provide a summary of a drug's effects [26, 48]. Such scales, however, are likely to measure a general effect [25]. Since drugs have effects in common, scales reflecting these patterns were also developed and are referred to as group variability scales [25]. For example, morphine and amphetamine, as contrasted with LSD, pentobarbital, chlorpromazine, pyrahexyl, and alcohol produced relatively greater effects on items that appear to signify euphoria; this pattern is referred to as the morphine-Benzedrine group variability (MBG) pattern. Some items such as itching were specific to only morphine (MG). Pentobarbital, chlorpromazine, and alcohol (PCAG pattern), in contrast, produced relatively greater effects on items suggesting low motivation, sedation and physical weakness. LSD produced effects of anxiety, depersonalization and other psychotomimetic effects that appeared relatively specific for it (LSD pattern). Some items contributed to more than one pattern. For instance, feeling weird is a general drug item and is on most of the empirical drug scales but it is also specific for LSD in the sense that LSD induced a greater weirdness effect than the other drugs tested. These scale names refer to the drugs tested at the time of the analysis.

Scales which measure the patterns of drug effects have greater power to differentiate drugs [25, 27]. Secondly, the meanings of items in the pattern scales are more homogeneous. Thus, items in the MBG scale signify more of a state of pleasantness to addicts than items in the empirical morphine scale that are not on the MBG scale [27]. This is an important difference as it has been suggested that the various effects produced by morphine are indicative of euphoria [52].

Using a discriminant function method the following drug conditions were distinguishable within the opiate addict group: no-drug or placebo, morphine, pentobarbital, cyclazocine and nalorphine, chlorpromazine, LSD, amphetamine, alcohol, opiate withdrawal, and chronic opiate [27]. Alcohol withdrawal, identified in alcoholics, can also be differentiated. While effects of these drugs can be differentiated, drug effects vary in similarity from identity for no-drug and placebo and for cyclazocine and nalorphine, similarity between alcohol and pentobarbital or morphine and amphetamine and to a sharp difference between opiate withdrawal and other drug conditions. It is emphasized that it is the pattern of effects over many scales that characterize a drug and not just a change on one scale.

Most studies employing the ARCI have used single scales such as the alcohol scale [1, 86] or subsamples of several scales such as MBG, PCAG, and LSD [55, 64]. The use of more than one scale provides the potential for differentiating between several drugs.

Chronic and Withdrawal Effects

Both the MMPI and ARCI show the chronic and withdrawal effects of opiates. Perhaps one reason for the effectiveness of the MMPI in these two areas is that the time dimension is less important. The effects found during the chronic phase in particular are felt by subjects over a long period of time. Addicts at the Addiction Research Center tested during the chronic phase of experimental addiction to morphine, heroin [32], and methadone [65] showed an increase on the MMPI Hypochondriasis scale. They also showed less motivation for physical, mental, social, and sexual activity on the ARCI as compared with their no-drug control.

Withdrawal effects were more marked than either acute or chronic effects. The neurotic traits of hypochondriasis, depression, hysteria, and psychasthenia were increased on the MMPI, but more psychologically morbid characteristics as measured by the Faking Bad and Paranoia scales were not significantly increased. The addicts reported feeling weak, tired, unmotivated, physically sick, tense, dysphoric, restless, impatient, uncooperative, irritable, reactive, and inefficient as measured by ARCI scales. Subjective reports on the ARCI of classic opiate withdrawal symptoms such as those reported by Himmelsbach [50] were markedly increased. No significant increase has been found on psychopathic scales of the MMPI or ARCI for acute, chronic, or withdrawal phases. However, during the withdrawal phase in particular, other types of pathology become greater relative to psychopathic traits. In terms of the types shown in table 1 they became more like subjects seeking a detoxification treatment (type 2) and less like drug-free addict prisoners (type 1).

Simulated Subjective Effects

The ARCI has been used to study simulated drug effects [27]. In this method subjects are asked to answer questions as they would under a drug. An alternative to this method is to hypnotize subjects [61]. Hypnosis in contrast to simulation of opiate withdrawal arouses visible turbulent emotional reactions in subjects. In the simulation of acute and chronic opiate effects, it is interesting to note that the effects were indistinguishable. This meant that subjects ascribed euphoria to both the chronic and the acute state; whereas, in actual experiments tolerance developed to euphoria and subjects became hypophoric [32, 65]. The overall simulated acute and chronic effect was more like the actual acute effect than the actual chronic effect. Subjects have been asked to simulate acute, day after, and withdrawal or come-down effects of heroin, marihuana, cocaine, goofballs (barbiturates), pep pills, and alcohol.

Differentiation of the acute effects among the major classes of drugs was found. But there was some similarity between morphine and marihuana, marihuana and amphetamine, amphetamine and cocaine, cocaine and LSD, barbiturates and alcohol, and between barbiturates, minor tranquilizers, and major tranquilizers.

Day-after effects of drugs were not highly differentiated, but a hangover effect was similar for goofballs and alcohol. Marihuana had no day-after effect as compared with the feeling upon getting up in the morning.

Withdrawal or come-down effects were differentiated somewhat. Marihuana produced no withdrawal effect or was similar to the feeling experienced on getting up in the morning. The withdrawal effects of goofballs and alcohol were similar. In addition there appeared to be a common element such as anxiety and feeling of sickness for withdrawal or of come-down from heroin, alcohol, goofballs, cocaine, and pep pills. Withdrawal effects which were present had some similarity with simulation of flu.

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Amphetamine Research at the Addiction Research Center

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Amphetamine was first studied at the Addiction Research Center by Himmelsbach, Cleek, and Lloyd. Their work, summarized in a U.S. Public Health Service report of 1944 [33], is detailed in their paper, "Studies on the Addiction Liability of Benzedrine Sulfate," which appears in this volume. Dr. Himmelsbach left the Center shortly after this work and manuscript was completed, and, for this reason, this paper has not previously been published. This was unfortunate because many of his findings, since replicated at other institutions as well as the Addiction Research Center, have proven to be quite relevant.

Of particular interest is Himmelsbach's observation that postaddicts allowed to self-administer amphetamine were likely to lose "control of their intake" and, in this circumstance, manifest important personality changes, including one patient who sustained a psychosis which resembled acute paranoid schizophrenia (Patient No. 590). He also noted that patients taken off amphetamine became depressed.

Himmelsbach was thus the first to observe an amphetamine psychosis under experimental conditions; however, the significance of this finding was not recognized for some time. Several years later, Connell [5], Bell [4], and Kalant [23] found that patients who became amphetamine-dependent usually went undetected until such time as they presented with a paranoid psychosis (which resembled and was often misdiagnosed as a functional mental disorder). Because the amphetamine psychosis was still disputed as being merely the activation of a latent psychosis, the drug was finally demonstrated as being psychotomimetic in a series of controlled studies [2, 3, 12, 13]. Himmelsbach's study can also be said to have anticipated the widespread abuse of amphetamine which was first reported among the inmates of several U.S. prisons during the late 1940's [20, 28] and, eventually, in many sectors of society [10, 24, 25].

Himmelsbach also speculated that in light of amphetamine's analgesic action, a mixture of amphetamine and morphine might have certain therapeutic advantages. Although not much used, the efficacy of this combination in certain clinical problems has since been demonstrated [1, 6, 7, 8, 9, 17]. More recently Jasinski and Nutt [21] have shown that although amphetamine antagonizes the respiratory depression and miosis produced by morphine, its effect on morphine euphoria is additive.

A number of other clinical studies of amphetamine have been conducted at the Addiction Research Center since Himmelsbach's initial work. Of considerable utility are the subjective test measures developed by Hill and Haertzen [16, 18, 19] for amphetamine as well as other drugs such as morphine, pentobarbital, LSD, and pyrahexyl. They also found that single doses of amphetamine produce subjective effects which are in some ways similar to that produced by single doses of morphine. Studies by Rosenberg et al. [32] demonstrated that while rapid tolerance develops to chronic amphetamine or to LSD-like hallucinogens, cross-tolerance does not develop between these drugs, suggesting that these two autonomic stimulants and psychotogens have different modes of action.

Martin et al. [27] initiated a series of studies aimed at developing methods for determining the abuse potential of amphetaminelike drugs. They demonstrated that although *d*-amphetamine, *d*-methamphetamine, phenmetrazine, methylphenidate, and *l*-ephedrine differed in terms of potency, all produced dose-related increases in blood pressure, respiratory rate, and epinephrine excretion, these paralleled by subjective changes, decreased appetite, and sleep time. A modest

TABLE 1

Relative potencies of various amphetamine-like drugs and ring-substituted congeners. Expressed as mg of *d*-amphetamine equivalent to 1 mg of the test drug.

Drug	MBG scale	Amphetamine scale	Benzedrine scale	Systolic B.P.	Diastolic B.P.	Caloric intake
d-Amphetamine	1	1	1	1	1	1
d-Methamphetamine†	---	.93	1.68	.92	1.49	1.19
Methylphenidate†	---	.48	.58	.31	.57	1.05
Phenmetrazine†	---	.21	.31	.26	.41	.43
Ephedrine†	---	.17	.17	.27	.11	.19
Diethylpropion‡	.15	.15	.18	.09	.12	.16
Benzphetamine‡	.20	.22	.24	.13	.13	.17
Phentermine‡	.405	.392	.445	414	.554	.162
Chlorphentermine‡	.020	.040	.024	.057	.056	.130
Fenfluramine‡	*	*	*	.056	.116	.226

† Comparison by the subcutaneous route.
‡ Comparison by the oral route.
* Valid assay was not obtained.

increase in pupil size was also noted. A subsequent study [11] has shown that amphetamine-induced mydriasis is more marked at 12–24 hours post drug when the depressive effects caused by amphetamine are more pronounced.

A number of other anorexigenic drugs have been studied for amphetamine-like properties [11, 14, 15, 22]. Diethylpropion, benzphetamine, and phentermine produced a pattern of physiological and subjective changes similar to that produced by amphetamine. Conversely, fenfluramine and chlorphentermine were discovered to produce sedation, dysphoria, and a pronounced initial mydriasis (relative potencies listed in table 1). Fenfluramine also induced a diazepam-reversible hallucinogenic episode in two subjects. These series of studies suggest that drugs with an amphetamine-like abuse potential can be identified experimentally in man.

Animal studies bearing on the mode of action of amphetamine have also been conducted at the Addiction Research Center. Amphetamine has been shown to facilitate the flexor reflex of the chronic spinal dog [26]. Because this effect is partially attenuated by phenoxybenzamine and reserpine, it appears that amphetamine exerts some of its actions, even at a spinal cord level, by the release of norepinephrine. However, it has other modes of action.

Risner [29] has shown that dogs will self-administer a number of psychostimulants, e.g., *d*-amphetamine, *l*-amphetamine, phenmetrazine, methylphenidate, and cocaine, often to doses which produce stereotypic behavior; however, methoxamine, a centrally acting alpha-adrenergic agonist [26] is not reinforcing [29]. Risner and Jones [30, 31] have further demonstrated that chlorpromazine and pimozide but not phenoxybenzamine increase operant behavior to obtain amphetamine. These interactions suggest that amphetamine self-administration in the dog involves a dopaminergic mechanism.

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Studies on the Addiction Liability of Benzedrine Sulfate

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From time to time concern has been expressed over the possibility of Benzedrine (*d,l*-amphetamine sulfate) being addictive [8, 10, 16, 21]. Other authors believe that this drug is not addictive [7, 13, 15]. Since some of the difference of opinion concerning this question arises from lack of uniformity in terminology, and in order to avoid misinterpretation of this report, it seems advisable to set forth definitions of terms used in discussing the problem and in describing our results.

Drug addiction constitutes a state of enslavement in which the individual has lost the power of self-control with reference to a drug, the habitual use of which is harmful to the individual and/or endangers the public health, morals, safety, or welfare. Addiction ordinarily embraces three interrelated phenomena which may be separated for purposes of discussion;

Tolerance means the reduced effect which accompanies repetitive administration of a drug, thus making it necessary to increase the dose to achieve or approximate original results;

Habituation signifies the psychic phenomenon of adaptation to the repetition of an effect. It may also be described as psychic dependence on or strong emotional attachment to a drug; and

Dependence indicates a physiologic disturbance resulting from prolonged administration of a drug which is manifested by the necessity for an adequate amount of the drug in the body for the maintenance of health. When the drug is withheld, signs and symptoms of illness occur which constitute an abstinence syndrome. The sine qua non of dependence is the appearance of an abstinence syndrome subsequent to withdrawal of the drug.

Euphoria simply means a sense of well-being or buoyancy.

The term "habit forming" is not pertinent since our pattern of life involves the acquisition of habits. This term does not distinguish between those habits which are helpful or innocuous and those in which the power of self-control is lost to the detriment of self and the public.

It is fairly common knowledge that Benzedrine has been employed by the laity for purposes of deriving a "lift," preventing fatigue and sleepiness, and offsetting the effects of over-indulgence in alcohol. Since such use would, in a sense, constitute abuse, it seems likely that if Benzedrine were significantly addictive, some clear-cut instances would have occurred as a result of its rather widespread availability during the past decade. This, with the possible exception of cases such as those reported by Hahne [10] and Friedenberg [8], has not been the case.

However, the rather serious curtailment in the availability of fashionable drugs of addiction, incident to the prosecution of the war, has led inveterate addicts to great reduction in dosage, obtaining relatively more from physicians, substitution of other drugs, and sometimes to "cure." Benzedrine is one of the drugs that has been tried as a substitute. It is understood that the Canadian Government, upon learning that addicts were "carrying on" with Benzedrine when other drugs were unavailable, made this drug a prescription item, not because it was considered to be addictive, but with a view of interfering with the continuity of traffic among "dope peddlers."

At this hospital Benzedrine was declared "contraband" upon learning that patients (postaddicts) were prevailing upon civilian personnel to bring them "inhalers." The strips contained therein were removed, placed in hot water, and the dissolved material taken orally, apparently causing euphoria.

In view of the above considerations it seemed advisable to attempt to ascertain the status of Benzedrine as a possible addictive agent.

Another possibility arises from the experimental finding of Goetzl et al. [9] that Benzedrine potentiates the analgetic power of morphine and possesses some analgetic properties per se. Should this carry over to man, the question would be raised as to the influence of Benzedrine on the addiction liability of morphine. Studies were carried out in an attempt to learn whether or not Benzedrine affects the pain threshold-raising effect of morphine in man, and to answer the above question.

The subjects for these studies were selected from a group of prisoner patients who had been abstinent from opiates for at least 6 months (postaddicts) and had sentences of sufficient length to preclude therapeutic contraindication. The Benzedrine sulfate used in these studies was furnished by the Smith, Kline & French Laboratories, Philadelphia, Pa.

On the Status of Benzedrine as a Drug of Choice Among Postaddicts

An attempt was made to learn where Benzedrine stands as a drug of choice among addicts by means of a questionnaire. Questionnaires were prepared in which ten drugs were listed in random order. In order to rule out the possibility of position-affecting results, four such lists were prepared and prior to distribution the lists were thoroughly mixed. The instructions were:

> Assuming that all the substances on the following list were freely available, check those you like best. Indicate your first, second, and third choices by placing the number in the proper square.
>
> Do not sign your name. This is a survey and names are not important.

The drugs listed were: Luminal (phenobarbital), coffee, morphine, cocaine, marihuana, Nembutal (pentobarbital, Na), Benzedrine (*d,l*-amphetamine sulfate), aspirin, Coca Cola, and alcohol.

The questionnaires were given to the guards just before going to work on the four o'clock shift. The guards passed them out to the patients while making count and collected and returned them within one-half hour. Thus, the effect of discussing the questionnaire and collaborating on results was minimized.

Three hundred and forty-five correctly marked questionnaires were returned. This is an adequate sample of the population. One hundred and forty-four questionnaires were returned on which the first, second, and third choices were not so indicated but were checked. Thus, data were secured from 489 addicts. The results are shown in table 1.

Morphine was the drug of choice; coffee was second; Coca Cola third. Results from the 144 questionnaires which did not indicate the order of choice gave coffee the highest percentage, and Coca Cola the second highest. Benzedrine was checked by only 14 out of the 489 who returned the questionnaires. This suggests that if Benzedrine is used by drug addicts it is only when other drugs are not available.

Administration of Benzedrine Sulfate to Postaddicts

This study was carried out for the purpose of learning what would happen if persons with inebriate impulse were to attempt to satisfy it by taking Benzedrine in self-chosen amounts over a period of 1 month. At the end of 1 month, the drug was abruptly withheld. Seven men out of a group of about seventy eligible for such studies agreed to participate. Insufficient material was available for Case No. 569; of the remaining six only one (Case No. 582) was able to complete the study. Two subjects tolerated the drug fairly well and seemed to enjoy it throughout. Five were unable to tolerate Benzedrine in the amounts given and either

Table 1

Status of Benzedrine as a drug of choice among postaddicts

Drug	First choice		Second choice		Third choice		Checked	
	No.	%	No.	%	No.	%	No.	%
Luminal	0	0	1	0.3	3	0.9	1	0.3
Coffee	82	23.7	112	32.5	70	20.3	117	33.3
Cocaine	8	2.3	55	15.9	17	4.9	13	3.7
Morphine	179	51.9	26	7.5	11	3.2	56	16.0
Marihuana	8	2.3	15	4.4	10	2.9	6	1.7
Nembutal	1	.3	16	4.6	14	4.1	1	0.3
Benzedrine	3	.9	5	1.4	6	1.7	0	0
Aspirin	1	.3	11	3.2	40	11.6	22	6.3
Coca Cola	41	11.9	78	22.6	92	26.7	107	30.5
Alcohol	22	6.4	26	7.5	82	23.8	28	7.9
Total	345	100.0	345	99.9	345	100.1	351	100.0

elected to discontinue it or interposed no objections when it was deemed advisable to terminate the study. Of these five, one (No. 590) developed a psychosis of the paranoid schizophrenic type, another (No. 594) developed a marked anxiety neurosis, and the remaining three (Nos. 601, 602, and 609) developed mild anxiety or panic reactions. All cleared up promptly after withdrawal.

None showed a frank abstinence syndrome. None complained of symptoms following withdrawal which were considered to be due to deprivation of Benzedrine. Only one asked for Benzedrine following its withdrawal. Subjects Nos. 590 and 594 obviously lost the power of self-control with reference to the drug; i.e., left to their own devices, they would have continued taking Benzedrine to their own further detriment.

Resumés of the clinical courses of these patients throughout the study are presented together with graphs (figures 1 and 2)[1] showing daily average rectal temperature, pulse rate, and respiratory rate; morning systolic blood pressure and stripped weight; total daily caloric intake, observed sleep, and dosage.

Resumés

Case No. 569

A. *Preliminary Observation Period:* The patient had a tinea infection of the feet and groin; otherwise was in good physical condition. His cooperation during this period was average.

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[1] Figures 1 and 2 have been lost.

B. *Administration of Benzedrine*: We had a supply of 1.5 grams of Benzedrine sulfate in solution for hypodermic use, and the patient was told that he could use up that supply as he saw fit but that we would interfere should it become apparent that he was doing himself harm. Medication was administered subcutaneously upon request of the patient.

No immediate effect was noted from the first dose. Later that day he was observed to be more active. He talked or was on the move continually. He perspired freely from the axillae. He was active all through the night. Hyperactivity continued throughout the next day and evening. He did not sleep the second night, continued to be very talkative, and said that he "just couldn't sleep." The third day he complained of getting no stimulation from the medication but talked continually on any subject to such an extent that other patients on the ward began to avoid him. While he continued to be talkative the evening of the third day, activity was observed to be diminished somewhat and he appeared to be tired. That night he slept about 5 hours; said he no longer got any "kick" from the medication and wanted the dosage increased. That day he appeared listless and did not talk quite as much. He said that he could not read as well without his glasses as he could before starting on medication, but that with glasses he noticed no difference. He continued to be talkative but less active. The fifth day there was no noticeable change in his condition. He slept 3 or 4 hours between midnight and 6:00 a.m. He spent most of the sixth day in bed, reading. Although in good spirits and cooperative his activity became reduced, and hyperactivity was observed only for about 2 hours after medication. On the eighth day he appeared tired and listless. Although he remained in bed he did not sleep much. On the ninth day he stated that he got very little stimulation from the medication. He wanted the dose increased. He spent the day in bed, was agreeable and in good spirits. He was no longer active after the medication. He was constipated, having reported only one bowel movement from the second through the eleventh day. During the remainder of the study he showed very little activity, even after medication. He stated that he had gone just about as far as he could and was afraid he would "have to quit before the medication gave out." Toward the end of the period he became very untidy about his person and quarters.

C. *Postmedication Period*: On the first day off there was some yawning and perspiration. He stated that he was glad it was over. He read until 3:30 a.m. and complained about his eyes bothering him. He was listless; had very little to say; and appeared tired and sleepy. On the second day off he was more active and did not appear so listless or tired. That night he was awake only 1 hour. On the third day he complained of feeling bad; appeared tired, sleepy, and listless as on the first day off. On the next day he said that he wished that he could get over that "low" feeling. He stated that his legs felt weak; that he had no "pep." On the evening of the fifth day off the patient complained of being "confused" and it was noted that he hadn't improved much. Although he ate and slept well and had no complaints, he did appear somewhat depressed and "pepless" on the sixth day. Postmedication observations were continued for a total of 15 days during which period he slowly improved.

Case No. 582

A. *Preliminary Observation Period*: Uneventful.

B. *Administration of Benzedrine*: The first day the patient reported getting a "drive" from the medication; pupils were dilated. He appeared to be enjoying the effect. On the second day he showed difficulty in enunciation, manifested chiefly as hesitation and stuttering. He was nauseated twice; felt as if he were "kicking a morphine habit." He appeared to be nervous, manifested by drumming his fingers, twitching his lips, and inability to relax. He became jittery and moved about a lot after medication. His actions were sudden with short pauses in between. He complained of dry mouth but apparently was enjoying the medication. On the sixth day he complained of "swimming" in the head when he lay down. He said that though he was thirsty he did not like to increase his fluid intake because it made him nauseated. He seemed less affected by medication but was still nervous. Able to derive no "pleasant effects" from 75 mg he took two 150-mg doses. No greater reactions were observed. His mood remained cheerful but he continued to give the impression of being nervous. This was most pronounced for about 2 hours after medication. Pupils were almost continually dilated. On the tenth day it was noted that his appearance was fine, mind clear, no stammering of speech, and pupils were normal. Tolerance was considered good. On the 12th day he complained of his hands itching; palms were reddened. The 14th day the patient stated that he no longer derived a "kick" from the medication. He began to spend a lot of time in bed. Again on the 19th day the same statement was made, but his general appearance and actions belied this. He appeared "jittery," could not stand still, and when in conversation his hands and arms were always moving. Speech consisted of a few words spoken rapidly, then a pause or stutter between bursts of talking. On the 22d day he complained of constipation and cramps in the stomach; was given an enema with good results. Only one bowel movement had been reported by the patient for the previous 5 days. On the 25th day the patient commented that he thought Benzedrine had made his sense of hearing much more acute;

that the effects of the medication lasted about an hour or an hour and a half; and that the reaction was similar to cocaine. On the last day the patient stayed in bed; was very inactive. Said he felt "rather low."

C. *Postmedication Period*: The first day off Benzedrine there was very little activity; he was not so nervous; spent most of the time in bed, reading; pupils were dilated. He complained of feeling "dry inside" and of his stomach being "weak." Second day: He complained of a "let down" feeling, was not "jittery" or nervous. Third day: Patient had a smothering spell at 3:00 a.m. Still complained of dry mouth. There was little activity but his spirits had improved. Fourth day: He complained of "floating" sensations and "horrible" dreams ("similar to kicking a dope habit") and of continual thirst. Fifth day: Patient still nervous, and "jittery" at times; complained of indigestion. Sixth day: He still complained of "horrible" dreams, but otherwise was much improved. Seventh day: Patient sleeping more soundly. No complaints.

Case No. 590

A. *Preliminary Observation Period*: Uneventful.

B. *Administration of Benzedrine*: This patient took 100 mg as his first dose and stated that he was "riding the crest." Activity was considerably decreased but he seemed more talkative. He complained of headache and slept little that night. He exhibited dilated pupils and gooseflesh. On the next day he continued to enjoy the medication; stating, "I believe there's something to this! It is difficult to obtain Benzedrine outside? I like morphine best." The second night he slept well; his pupils were not dilated. The third day he claimed to have obtained no "drive" from the medication but gooseflesh was very pronounced. He took 420 mg that day, slept fairly well that night, but it was observed the next morning that he had a peculiar expression on his face. On the fourth night it was noticed that he groaned and gritted his teeth while asleep. On the fifth day he exhibited a tremor. He took 400 mg and obtained considerable "kick." On the seventh day his condition appeared the same: intoxicated, very sociable, but somewhat irritable in the morning. There was not much activity; his pupils were dilated and he complained of a dry mouth. That afternoon he was observed lying in bed, shaking his head, saying, "No, no." He ate very little dinner and kept shaking his head, chanting "No, no." He appeared to be afraid of something; he asked for Benzedrine but in view of his condition was given normal saline instead. He then said he was feeling fine.

C. *Postmedication Period*: Before being awakened the next morning he was observed to be groaning as if in great pain. He had a painful expression on his face and was perspiring freely. When aroused he said he was sure he had not been getting Benzedrine and "did not know what to think about it." He appeared frightened; it was obvious that he was quite confused. For example, he thought he had been given a "test" and said that if we were through he would return to his dormitory. He was given an infusion of 10 percent dextrose in normal saline. He became quite nervous that evening and requested that he be locked up for protection, stating that, "They are after me." He would not drink lemonade because he was sure there was poison in it. He thought one of the patients on the ward was planning to kill him and discussed the matter quite frankly and unemotionally with this patient. Later he took a flow bath and another infusion; he then seemed improved. He slept most of the night and when awake would sometimes talk sensibly but at other times was confused. His pulse was irregular, respiration deep and labored. The next day his speech was incoherent. His paranoid ideas continued. One remarkable incident was that he refused to take a dose of morphine prescribed for him. His affect was flat, motor activity slowed down, but insomnia continued. He was given paraldehyde. When awakened next day he was obviously improved. It became apparent that he did not remember anything that had happened for the past few days. His contact with reality was interrupted by periods of confusion; occasionally he would relapse to his previous chant of, "No, no. It's not right." Paraldehyde was repeated and he slept well. On the next day though he was quite nervous, fearful and worried; periods of confusion occurred from time to time. He still tended to decline medication, but could be persuaded to take it (e.g., sedatives, infusions, vitamins, and fruit juices). He continued to improve some each day, slept a great deal, but when awake he worried about what he might have done or said. On the seventh day off Benzedrine he stated that he remembered nothing after the first dose.

Case No. 594

A. Preliminary Observation Period: Uneventful except for a few periods of irritability.

B. Administration of Benzedrine: At first he did not seem to be nervous, but was quite active and talkative, much more sociable than normally, and exceptionally cooperative. He stated that he enjoyed working and that he would like to have more to do; saying, "There is no one in the world who feels as good as I." This feeling of euphoria, increased cooperativeness, and productive activity continued, together with insomnia, throughout the first day. On the third day the patient began taking minute doses at about 2-hour intervals. At this time it was noted that he was slightly disoriented, and that night he became very nervous and confused, even refusing to take the sedative ordered for him. The drug was discontinued. His manner became very disagreeable and he resented observation. Later that night he exhibited considerable concern about his condition and agreed to take paraldehyde. He went to sleep promptly thereafter and when he awakened about noon the next day his mind seemed clear, but he was still very nervous and anxious. It was noticed that he had developed blisters in the palms of his hands caused by clenching them frequently and intensely while stimulated by Benzedrine. He was given 15 mg of morphine and seemed to improve shortly thereafter. That night he again became very nervous and paraldehyde was repeated. He apologized for his disagreeable behavior of the previous evening. The next day he was still somewhat nervous. He asked for morphine and was somewhat grouchy after this was refused. He improved slowly and was anxious to try Benzedrine again as soon as he felt strong enough. Administration of Benzedrine was resumed on a restricted schedule. Shortly thereafter he said he felt fine; he was pleasant and agreeable but he evinced a certain amount of disappointment in the size of the dosage. Later he complained of "roaring in the head and ears," and said the medication was hitting him "just right, not too strong or too weak." He appeared comfortable and contented. His tolerance seemed adequate and he said he was "well satisfied." Later he asked that his dosage not be increased and on the fifth day he became very nervous for a short while. It was observed that he was becoming more seclusive each day and having periods of irritability. His activity decreased except for short periods of industriousness following administration of the drug. On the eighth day he complained of a "prickly and annoying feeling" around his face and head. He was obviously quite nervous and that night it was observed that he talked in his sleep. He exhibited occasional episodes of confusion and questioned the fact that he was getting Benzedrine. He said he felt "fine" in the morning but in the afternoon and late evening he felt "horrible." On the tenth day he was sullen, and stated that he no longer derived any "kick" from the medication. He did not want to attend the movies, complained of feeling "low," his humor was bad, and he wanted to "check out." On the 13th day the dosage was increased to 45 mg b.i.d. He slept less, became more nervous and irritable. It was observed that he became startled quite easily by unexpected noises. He stated that he had been having "horrible dreams." His pulse was irregular. The dosage was reduced to 40 mg twice daily; he became less active, more seclusive, and his pulse continued to be irregular. He stated that he got no effect from the medication, that he had "developed a tolerance," and "could take any amount." His mood again became agreeable when the dosage was increased to 60 mg b.i.d. He became more sociable, active, and talkative, but slept less. On the 15th day he became worried about the way his head felt, stating that he had "cold flashes" in the top and center of his head and a "sense of pressure in the center." Benzedrine was discontinued.

C. Postmedication Period: He spent the first day in his room, was in good spirits, and slept a great deal. The next day he was in low spirits and said he did not feel well, had little to say, and stayed in his room. The third day he showed no activity, appeared depressed, talked in his sleep, and complained of headache. He asked to be checked out as soon as possible. Condition the same on the fourth day; he was given morphine. He then became very active, his spirits improved. He cleaned his person and quarters.

Case No. 601

A. Preliminary Observation Period: Patient said that he had used a lot of Benzedrine, liked it, and was able to tolerate it well. The preliminary observation period was uneventful.

B. Administration of Benzedrine: He considered the initial dose inadequate. The next day it was reported that his pulse was irregular but he seemed satisfied and enjoyed the medication. He complained of headache; was more irritable than usual. Disappointment over the inadequacy of the dosage continued. On the third day he took a total of 80 mg which he considered adequate. He was in good spirits, and pleased. He became ebullient, loquacious, and showed gooseflesh. On the fifth day he took only 30 mg, stating that he had a "queer and dizzy feeling," and that he was afraid to take any more until he found out how he would react to what he had already taken. He took no medication on the sixth day and expressed some fear about the drug. On the seventh day he decided to switch from the parenteral to the oral route. He obtained a pleasant effect from 30 mg orally, stating that the medication was better orally. He thought he could tolerate it better. On the 11th day he complained of a dry mouth. He seemed content and apparently was tolerating the medication satisfactorily. On the 13th day he took 130 mg; spent the greater part of the day in bed; his face was flushed; conversation intelligent; he was happy and in a humorous mood. On the 15th day he again became fearful of the drug. He had "hot" flashes around his forehead, his temples, and the back of his neck; he was less jovial and his pulse was irregular. He became more seclusive. On the 17th day it was suggested that he discontinue the medication. He readily agreed to do this, feeling that continuation would probably be harmful.

C. Postmedication Period: The first 2 days after withdrawal were spent in bed. On the third day he got up and around, was in good humor, and no longer anxious.

Case No. 602

A. Preliminary Observation Period: Uneventful.

B. Administration of Benzedrine: Initially, he complained about the inadequacy of the dosage and persistent headache but was in a good mood. On the second day he admitted "feeling" the medication. He stated that he was afraid of it. On the fourth day he took 100 mg and apparently enjoyed it. The next morning, however, he became a bit anxious and asked to have his dosage reduced. He complained of a "full" sensation in his head and a "dead" sensation in his arms. On the sixth day he took no medication. The seventh day he took the drug by mouth and had a pleasant effect from it. That afternoon, however, he expressed definite fear about continuing the study.

C. *Postmedication Period*: Observations were continued for 5 days after the last dose. Anxiety disappeared on the second day after withdrawal.

Case No. 609

A. *Preliminary Observation Period*: Prior to beginning the study, the patient developed a sore throat, fever, and headache and was treated with sulfathiazole. Following recovery, preliminary observations were continued until a total of one week "normal" data were obtained.

B. *Administration of Benzedrine*: The patient stated that he got very little reaction from the first dose but that the effect he did notice was similar to that of cocaine. He spent the day in bed, sleeping; was somewhat more talkative than usual when awake. The next day he was more active and in much better spirits than usual. He spent considerable time cleaning his person and quarters; was very talkative. He stated that since he had started on Benzedrine his sexual desires had increased so much that he needed a cold towel to reduce a priapism. He complained that his mouth was dry; slept fairly well; had no other complaints. The dosage was increased slowly; tolerance seemed good. He seemed to enjoy himself; his mood was stimulated; and he was quite garrulous. On the fifth day he complained of "leg pains." On the sixth day he was less talkative and was somewhat worried about his "affairs on the outside." His activity had declined; he said he was feeling "only fair." The seventh day he was much less cheerful and talkative; refused his medication; said he was getting afraid of it; thought he would take none whatever the next day. On the eighth day he complained of "hot" and "cold" flashes; said his heart felt "depressed." He did not sleep well and he worried about his condition. He considered the drug to be "rough," that it would "kick you around." On the ninth day he took 10 mg; his mood improved, but he elected to take no more.

C. *Postmedication Period*: Patient spent a great deal of time in bed following discontinuation of the medication, but except for headache had no complaints. He seemed tired and depressed, less active than prior to Benzedrine administration. He improved slowly.

Effects of Morphine and Benzedrine on the Pain Threshold of Postaddicts

Since Goetzl et al. [9] have shown that Benzedrine has pain threshold-raising properties and potentiates this effect of morphine in dogs, it was considered appropriate to study this phenomenon in man.

Should Benzedrine potentiate the analgetic effect of morphine in man, this combination could assume clinical importance, for it might be expected that Benzedrine would tend to antidote certain other aspects of morphine action. If this latter possibility were not realized, the greater reduction in dosage of morphine achieved by the former might of itself reduce the hazards inherent in the clinical use of morphine.

Methods

Subjects: The 12 subjects used in these studies were postaddicts. All volunteered for the study and were well trained in the recognition of the end point as described by Hardy et al.[11].

Drugs: The effect on the pain threshold of normal saline (1 cm^3); morphine (30 mg); Benzedrine (30 mg); and, morphine (30 mg) and Benzedrine (20 mg) together were tested. All medication was given subcutaneously after the determination of the preinjection threshold (at least five readings). In no case was the subject told the amount or the drug he received. Following administration of a drug, readings were taken every 15 minutes for 2 hours. An interval of at least 2 weeks elapsed between successive doses. Each subject was tested on all four drugs.

Apparatus: The apparatus used in the determination of the pain threshold was essentially that described by Hardy et al. [11]. It differed in the following respects:

1. The apparatus was constructed so that the subject rested in the recumbent position instead of the sitting. This was done to minimize the effects of tension, strain, and fatigue.
2. A flap of soft rubber hung below the aperture to make sure that the patient's forehead was at the focal point of the beam. This flap was not allowed to touch the patient.
3. A voltage-regulating transformer was used which made power line fluctuations negligible.
4. The exposure was controlled by a hand-operated shutter and a revolving disc with an opening cut in it to allow a 3-second interval.
5. Readings were made by means of a wattmeter as described by Andrews [1].

Results

The results are shown in table 2, in which the effects of normal saline, morphine, Benzedrine, and morphine and Benzedrine together are compared. Time action curves were drawn through the median responses. The areas included within these curves and the base lines for 2 hours after medication were measured with a planimeter. These areas were converted into percent-hours. The method used has been described by Andrews [1] as a means for measuring the total pain threshold effects. The values obtained are shown in table 2.

The refractoriness of the postaddict to the pain threshold-raising effect of morphine (but not to its analgetic action) has been described by Andrews [1]. The results described above are consistent with his findings.

The results with normal saline confirm the assumption that no alteration of pain threshold occurs over a few hours. These results also indicate that deviations from the threshold in these particular subjects have probable significance.

Benzedrine per se caused a slight elevation of the pain threshold.

Since the effect with morphine and Benzedrine together was greater than the added values for these drugs alone, potentiation is suggested. Slaughter and Munsell [18] have reported that a cholinergic substance (Prostigmin) potentiates the pain threshold-raising action of morphine. It seems hardly likely a priori that both cholinergic and adrenergic compounds would potentiate this effect of morphine. It should not be assumed from these results that Benzedrine will potentiate the *analgetic* effect of morphine, but these results do suggest that this possibility might be worthy of further study.

A Comparison of the Dependence Liability of Morphine With That of Morphine and Benzedrine Together

If it should be established that morphine when given in conjunction with Benzedrine produces more analgesia than morphine alone, the question would be raised as to the effect of Benzedrine on the addiction liability of morphine. The following study was carried out in an attempt to answer that question.

Thirty postaddicts were used as subjects. They were studied in three pairs of groups matched as follows: Groups VII-L-2, 4, and 6, after one week of preliminary observation, were given morphine together with Benzedrine for 30 days. Withdrawal was abrupt and complete. Observa-

TABLE 2

Comparison of effects of normal saline, morphine, Benzedrine, and morphine-Benzedrine on pain threshold

Medication	Percent-hours
Normal saline	0.00
Morphine	21.00
Benzedrine	7.25
Morphine and Benzedrine	32.10

tions were continued for 7 days of abstinence. Groups VII-L-1, 3, and 5, served as controls; i.e., they received identical amounts of morphine as did the corresponding groups, but were given no Benzedrine. Each group consisted of 5 subjects. The dosage schedules were as shown in table 3.

The daily amount was divided into four approximately equal doses and administered subcutaneously at 6 and 11 a.m., 5 and 10 p.m. The study was carried out on a ward devoted exclusively to clinical research. Nursing care, observation, and supervision were maintained 24 hours per day by experienced personnel especially trained for such work. Abstinence syndrome intensities were scored by the point system [12].

Results

Brief descriptions of the clinical courses of the six groups are given below. In addition the group daily averages for temperature (rectal), pulse, respiration, a.m. systolic blood pressure, a.m. weight (shown as deviations in kg from weight on the first day of preliminary observation), total caloric intake, hours of sleep per 24, and dosage are presented in figure 3.[1] The abstinence syndromes are compared in table 4.

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[1] Figure 3 has been lost.

TABLE 3

Dosage schedule for comparison of dependence liability—Morphine versus morphine-Benzedrine

		Dosage	
Group	Kind	Morphine	Benzedrine
VII-L-1	Fixed level	60 mg daily	None
VII-L-2	Fixed level	60 mg daily	20 mg daily
VII-L-3	Fixed ascending	20 to 120 mg daily	None
VII-L-4	Fixed ascending	20 to 120 mg daily	10 to 60 mg daily
VII-L-5	Ad libitum	52 to 304 mg daily	None
VII-L-6	Ad libitum	52 to 304 mg daily	26 to 152 mg daily

TABLE 4

Total abstinence syndrome

Group	Point-days
VII-L-1	137
VII-L-2	116
VII-L-3	141
VII-L-4	138
VII-L-5	251
VII-L-6	147

Clinical Courses of the Groups While Receiving Drugs

VII-L-1. Loaded and hyperactive at first. Nausea and emesis, dyspepsia, and constipation throughout. Skin dry and irritated, with itching. Vegetated the last 2 to 3 weeks.

VII-L-2. About same as above with some insomnia, nervousness, irritability, "cocaine horrors," and one case of toxic psychosis which cleared up promptly following withdrawal.

VII-L-3. Loaded at first. Fairly comfortable and happy throughout. Only one became very inactive; the rest slowed down somewhat. No G.I. upsets, constipation, or skin trouble.

VII-L-4. Loaded at first. All but one slowed considerably. Dry mouth and skin; some insomnia and anorexia. All subjects but one were glad when the study was over! One had very poor tolerance for Benzedrine; one had very good tolerance for this drug.

VII-L-5. At first, increased activity and talk, with euphoria; later, slowed down somewhat but happy, "loaded" and "on the nod." This latter state was fairly uniform. Little or no G.I. or skin trouble.

VII-L-6. All stimulated at outset; thereafter there was considerable variation in tolerance for and reaction to the mixture. One was intolerant and sick throughout, with anorexia, nausea, and vomiting; one was stimulated, tolerant, and fairly happy—with insomnia and increased psychomotor activity, twitching and jerks; another slowed down and "coasted." The other two varied within the above limits. All had skin trouble and dry mouth.

The areas beneath the abstinence syndrome intensity curves were measured and converted into point-days. These values indicate that in each instance the morphine abstinence syndrome was more severe than that which followed withdrawal of the corresponding morphine and Benzedrine.

The difference between groups VII-L-1 and 2 and between groups VII-L-3 and 4 as shown in table 4 are so slight that they probably have no significance. However, the difference between groups VII-L-5 and 6 is great.

These results in the lower dose ranges indicate that while Benzedrine may make morphine less desirable to the individual, it does not significantly affect the development of physical dependence. However, in the higher dose range, Benzedrine significantly interferes with the development of physical dependence on morphine.

Psychological Studies

One frequently mentioned effect attributed to Benzedrine sulfate is an improvement of mood. This includes a feeling of increased energy, relief from fatigue, increased confidence, loquacity, optimism, and euphoria. Turner and Carl [20] devised a method for measuring subjective effects and concluded that the improvement of mood usually caused by Benzedrine is frequently proportionate to the amount ingested, but that the optimal dose varies with the individual. Scores of psychological tests (ergograph, reaction time, tapping, grip, hand steadiness) have been reported to be improved by Benzedrine [19]. However, it seems to have no effect on the attention span for letters or colors [3, 4].

Numerous groups of normal and mentally deficient persons have been given various mental tests after taking Benzedrine [6]. Errors were reduced about 10 percent as compared to the control groups. Improvement is attributed to the favorable effect on the emotional attitude of the subject rather than to any real facilitation of or increase in mental capacity. Barmack [2] reported that 10 mg of Benzedrine did not improve scores on the Otis Intelligence Test given to college students.

The purpose of the present study was to determine what psychological effects follow ingestion of Benzedrine. Three groups were studied. The first group consisted of the 7 patients who agreed to take Benzedrine in self-chosen amounts for 1 month. Groups 2 and 3 consisted of 15 patients each who received morphine or morphine and Benzedrine together according to the dosage schedule described previously. These subgroups were combined into the two groups. The morphine group is referred to as group "M" and the Morphine-Benzedrine group as group "M-B."

Procedure

A battery of tests commonly used in psychometric testing was administered at predetermined intervals throughout the study. The battery was given during the preliminary observation period on the 5th or 6th day after admission to the ward. On the 19th or 20th day of administration of the drug the battery was repeated and again after withdrawal on the day before the patient left the ward. The test battery included:

1. The Rorschach
2. Otis S. A. Test
3. Memory Span for Digits (forward)
4. Koh's Blocks
5. Arithmetic Test
6. Perseveration Test
7. Seven Simple Tests of Coordination

Descriptions of the various tests are given in the results.

Results

A. Benzedrine Group:

Of the seven patients who agreed to take Benzedrine in self-chosen dosages, only one was able to complete the study. Insufficient drug was available for another. The remaining five were unable to tolerate Benzedrine in the amounts chosen and elected to discontinue medication or it was advisable to terminate the study.

The patient who completed the study (Case No. 582) was 31 years of age and had previously used Benzedrine in addition to heroin, opium, and Pantopon. Rorschach analysis revealed him to be fairly stable emotionally. He was unable to complete tests because of poor coordination and nervousness. His actions were abrupt and speech was hesitant. He could not write legibly and could not sit still long enough to complete any test. On the sixth day after medication was discontinued his test performance compared favorably with that during the preliminary period. At that time he apologized for his inability to perform better during the administration of the drug.

Patient No. 590, who has 33 years of age and had used heroin and cocaine, developed either a toxic psychosis of the schizophrenic paranoid type or had a psychotic episode precipitated by the medication. Analysis of Rorschach record previous to study revealed suspiciousness, anxiety, and paranoid trends.

During the administration of the drug he became confused and developed paranoid ideas. He doubted that he was getting Benzedrine and thought that the patients were against him and trying to poison him. He became negativistic and his contact with reality was poor. Three days after Benzedrine was discontinued he was less confused and was in better contact. He was still suspicious and worried somewhat because he was unable to remember what he had done or said for the past few days. On the seventh day after medication was discontinued he seemed mentally alert and realized that he had been out of contact. He was then discharged from the ward.

Patient No. 594, 44 years of age, developed a marked anxiety neurosis. He had used cocaine, heroin, Dilaudid, and Demerol. Analysis of Rorschach revealed a psychoneurotic individual with indications of anxiety and tension.

As medication continued he became increasingly restless, excitable, and out of contact with reality. He developed blisters in the palms of his hands from clenching them so many times while stimulated by Benzedrine. The drug was discontinued. He seemed to remember little of what had happened. After recovery he was again started on Benzedrine on a controlled dosage. His mood was improved and he was less irritable. When Benzedrine was withdrawn his behavior and mood remained about the same. During his stay on the ward he never associated with the other patients but spent most of his time in his room.

The other patients (Nos. 601, 602, 609) developed mild anxiety or panic reaction states which cleared up promptly after withdrawal. Rorschach analysis revealed that these patients were fairly stable emotionally.

Of the seven cases studied in this group desirable changes (lessening of depression, increased feelings of energy, sociability) were only temporary and as medication continued undesirable feelings of restlessness, agitation, and fear were noted.

Myerson [14] noted that frequently he obtained in normal individuals, in mildly depressed, and in psychoneurotic persons, and in normally fatigued persons, certain distinctly beneficial results following the administration of Benzedrine. It appeared that in persons normal and mildly abnormal, Benzedrine was beneficial because it permitted the existence of a physical or mental state which was conducive to a more adequate social adjustment. Individuals in depressed, restless, agitated, fearful states were relieved of these symptoms to a great extent so long as the use of Benzedrine was continued, but they reappeared upon discontinuation.

Schube et al. [17] investigated the effect of Benzedrine on those individuals who possessed major psychoses sufficient to necessitate hospital treatment. Of the 80 cases studied there was no improvement in any. In 15 of the 80 cases there was temporary accentuation of the psychosis.

B. Morphine and Morphine-Benzedrine Groups:

1. *Otis S. A. Test.* The Otis S. A. Test is a conventional "intelligence" test of the self-administering type with a ½-hour time limit. The same form was used for the three testing sessions. It is generally supposed that practice effect is negligible. Scores on this test may be converted directly into I.Q. ratings for adults by the addition of a constant. The data presented in table 5 are in terms of mean I.Q.'s for the two groups.

TABLE 5

Mean I.Q. test results

Group	Before	On	After
Morphine	93.0	90.0	95.0
Morphine-Benzedrine	88.0	93.0	89.0

From table 5 it is seen that group M showed some loss, suggesting a decrease in efficiency when physical dependence occurs. After withdrawal there was an increase which may be accounted for by a practice effect. Group M-B improved while on medication. The difference between the two groups suggests that Benzedrine had some effect on increasing speed since this was a *time* test and overcame, to some extent, the general slowing down which morphine causes.

2. *Memory for Digits (forward).* This is the conventional auditory test in which a list of digits is read, arranged to yield a point score with a maximum of 45 points for the whole test. There are 15 items with 3 in each of 5 groups, running from a span of 5 to a span of 9. One point credit was given for each item at the 5-span level and so on to 5 points for the 9-span level. The same form was used in each of the three administrations. The means for the two groups are given in table 6.

From these results there is some reason for concluding that function on this test was influenced favorably by the morphine-Benzedrine combination.

3. *Koh's Blocks.* This is a performance test consisting of 16 specially colored cubes. These cubes are given the subject with the request to put 4 or 9 or 16 of them together and have the design on the tops resemble the design indicated on the card set before him. There are 17 designs. Performance on the test is a function of the ability to analyze and synthesize. It may be utilized as a measure of intelligence, but is chiefly of importance as a corroborative and supplementary source of information.

Each design has a time limit and the maximum was recorded when the subject failed to complete the designs. Errors were recorded when the subject was satisfied with incorrect designs. When one or more blocks

TABLE 6

Digit memory auditory test—Mean point scores

Group	Before	On	After
Morphine	11.6	10.8	12.0
Morphine-Benzedrine	8.9	10.5	10.2

were wrong one error was counted for each incorrect block. Table 7 shows mean times in seconds and errors for the two groups.

From table 7 it is seen that group M-B shows a decrease in time for completion of the designs. Morphine-Benzedrine appears to have increased speed and efficiency as measured by relative errors. Group M-B worked faster, making only as many errors as on the first performance. After withdrawal both groups showed increases in speed over initial performance.

4. Arithmetic Test. The arithmetic test consists of a column of simple addition, multiplication, and subtraction problems. Time for completion was scored and the number of errors calculated. Since 5 of the 15 patients in group M-B were receiving morphine-Benzedrine in self-chosen amounts, the possibility of these 5 having greater influence on the mean data and thus accounting for changes which were representative of those 5 rather than the whole group was considered. Thus group M-B was broken down in sub-groups of 10 and 5. Results are shown in table 8.

These data reveal changes in favor of group M-B. The changes still hold when the group is broken down into two groups of 10 and 5 patients respectively. No increase in efficiency as measured by errors is noted.

5. Perseveration. The arithmetic test served as a perseveration test by adding a fourth column of problems in which addition, subtraction, and multiplication were jumbled. The perseveration score was computed by subtracting the expected time score for column 4, which was based on the time taken for the other three columns, from the actual time taken for column 4. High scores are therefore associated with increased perseveration, i.e., greater difficulty in changing from one mental set to another. Brown and Partington [5] reported greater perseveration for postaddicts as compared to a control group of hospital attendants.

Mean scores for these data for groups M and M-B and for groups M-B with the 5 patients on self-chosen amounts of morphine-Benzedrine are shown in table 9.

TABLE 7

Koh's blocks test—Mean times and errors

	Time (seconds)			Errors		
Group	Before	On	After	Before	On	After
Morphine	98.0	100.0	81.0	2.2	2.2	1.0
Morphine-Benzedrine	103.0	99.0	83.0	3.7	3.1	3.0

TABLE 8

Arithmetic test—Mean times and errors

	Time (seconds)			Errors		
Group	Before	On	After	Before	On	After
Morphine	92.0	101.0	99.0	2.3	3.6	2.0
Morphine-Benzedrine	112.0	102.0	99.0	4.0	5.0	6.4
Morphine-Benzedrine (10)	118.0	107.0	100.0	3.0	4.8	4.5
Morphine-Benzedrine (5)	99.0	92.0	96.0	6.4	7.6	6.1

TABLE 9

Perseveration test—Mean difference scores (times)

Group	Before	On	After
Morphine	22	25	19
Morphine-Benzedrine	23	22	15
Morphine-Benzedrine (10)	21	22	23
Morphine-Benzedrine (5)	29	23	23

The data shown in table 9 for groups M and M-B indicate no significant differences between the two groups. The 5 patients on larger doses of Benzedrine show some improvement which may be attributed to the effect of Benzedrine.

6. *Coordination.* Subjects were requested to fill in blanks with lines, geometrical figures, or letters. They were instructed that no lines could be crossed. Coordination was measured in seconds for completion. Mean results for these data are shown in table 10.

These data suggest that coordination was influenced adversely by the medication. It is evident that speed alone was not being measured since on tests in which speed was the chief factor, group M-B improved.

7. *Rorschach Analysis.* This technique consists of 10 ink-blot pictures which are used as stimulus material. Subjects are instructed to look at each picture as it is shown and tell what it reminds them of or what it resembles. Rorschach records are scored according to certain characteristics in concept formation. This technique reveals the basic organization of the personality structure, including affective and cognitive features of mental life. Records were analyzed and results are shown in table 11.

For group M there seems to be a slight decrease in anxiety as indicated by a decrease in shading responses and increases in human responses. Group M-B shows a decrease in constriction indicated by a decrease in

TABLE 10

Coordination test—Mean times

Group	Time (seconds)		
	Before	On	After
Morphine	653	682	606
Morphine-Benzedrine	627	662	580

TABLE 11

Rorschach Analysis—Discreet responses

Group	Before		On		After	
	M	M-B	M	M-B	M	M-B
Responses	15.0	15.0	13.0	16.0	12.0	17.0
Wholes	6.0	4.0	5.0	4.0	4.0	5.0
Details	8.0	11.0	8.0	11.0	7.0	11.0
Rare Details	0.6	0.3	0.6	0.2	0.4	0.2
Movement	1.4	0.8	1.1	0.8	0.7	1.2
Animal Movement	0.2	0.8	0.7	0.4	0.5	0.5
Pure Color	0.2	0.6	0.2	0.4	0.2	0.8
Color Sum	1.1	2.0	1.6	1.2	1.0	3.2
Color Form	0.2	0.6	0.1	0.4	0	1.2
Form Color	1.1	1.5	1.7	1.3	1.5	1.4
White Space	0.4	0.9	0.5	0.4	0.5	0.3
Shading	3.0	3.0	2.5	2.5	2.8	2.8
Human	1.3	0.7	1.9	1.0	1.9	1.3
Human Detail	0.5	0.3	0.8	0.8	1.5	0.5
Anatomy	2.4	1.6	0.9	1.7	1.5	0.8
F+%	92.0	94.0	87.0	94.0	85.0	99.0
F Attachments*	61.0	57.0	47.0	61.0	43.0	63.0
A%	54.0	48.0	56.0	36.0	55.0	33.0
$\frac{R\ 8, 9, 10}{R}$	36.0	30.0	33.0	33.0	32.0	51.0

*Refers to the percentage of responses in which only the form of the blot entered as a determinant. In the scoring system of Klopfer this would be referred to as F percent. The formula is:

$$\frac{(F+)+(F)+(F-)}{R}$$

F +%. Change in A % for group M-B from 48 to 36 is another indication of decreased intra-psychic constriction. It appears that morphine and morphine-Benzedrine act to reduce emotional tension as indicated by signs of constriction and depression in the Rorschach, and that Benzedrine given with morphine caused no significant changes that could be attributed to the combination of the drugs.

Discussion and Summary

Curtailment in the availability of fashionable drugs of addiction has led to the substitution of Benzedrine by some addicts. In view of this it seemed advisable to study Benzedrine from the standpoint of its addiction liability. A survey made by means of a questionnaire indicated that the incarcerated postaddicts of this hospital place Benzedrine last in preference in a group of ten drugs.

To study the addiction liability of Benzedrine, it was given to seven patients who agreed to take the drug ad libitum for 1 month. Of this group only one was able to complete the study. Studies were interrupted in the others because of the development of psychoses, anxiety neuroses, and panic states. Some tolerance developed; frank habituation (psychic dependence) occurred in only one patient, the antithesis in the others; none developed physical dependence. The power of self-control with reference to the drug was lost by two who became psychotic, but this may be interpreted to signify clouded judgment rather than an overpowering biological need for the drug. The maximum dose attained by any patient was 1 gram per day. These patients were unable to complete psychological tests because of poor coordination and nervousness. Desirable changes (lessening of depression, increased feelings of energy and sociability) were only temporary and as medication continued undesirable feelings of restlessness, agitation, and fear were noted. Analyses of Rorschach records previous to study revealed evidence of emotional instability and psychoneurotic personalities. Psychological studies reported in the literature [20] using normal subjects and psychoneurotic patients to whom smaller dosages of Benzedrine were administered showed improvement in scores on psycho-physical tests.

It has been shown experimentally in dogs [9] that Benzedrine potentiates the pain threshold-raising action of morphine and possesses similar properties of its own. In 12 trained postaddict subjects it was found that Benzedrine per se caused a slight elevation of pain threshold and that morphine given with Benzedrine had a greater effect than either drug alone or the sum of their effects. This improved effect does not necessarily imply that Benzedrine will potentiate the analgetic effect of morphine. However, should such potentiation obtain, the question would be raised as to the influence of Benzedrine on the addiction liability of morphine. Hence three paired groups of 5 men each were studied as follows: Two groups received 60 mg morphine per day for 1 month. One group was given 20 mg Benzedrine per day with the morphine. No difference in abstinence syndromes was noted. Two other groups were given ascending amounts of morphine (20 to 120 mg per day for 30 days). One of these groups received 10 to 60 mg Benzedrine with the morphine. No difference in the abstinence syndromes was noted. Of the last two groups, one received morphine-Benzedrine in 2–1 ratio ad libitum for 30 days, and the other received identical amounts of morphine without Benzedrine. The abstinence syndrome of the latter group was about twice as severe as that of the former. It would appear, therefore, that Benzedrine does not contribute to the addiction liability of morphine in amounts which might be given clinically, and that in excessive amounts it reduces the power of morphine to cause physical dependence.

The above morphine-Benzedrine groups were superior in performance to the corresponding morphine groups on a battery of various psychometric tests. These differences cannot be explained by practice effects or initial differences, but may be attributed to the effect of Benzedrine on overcoming the general slowing which results when physical dependence on morphine occurs. Rorschach analyses showed no difference attributable to the morphine-Benzedrine combination.

Conclusions

It seems unlikely that abuse of Benzedrine will become a clinico-social problem for although tolerance is developed for the drug no evidence of physical dependence or strong habituation was encountered.

Benzedrine seems to potentiate the pain threshold-raising action of morphine. Should this carry over to analgesia per se, the administration of such a mixture in the practice of medicine will be attended with less addiction hazard than equal amounts of morphine per se because of reduction in dosage.

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Round Table on Measurement of Subjective Responses to Psychoactive Drugs and Personality Characteristics of Narcotic Addicts (Left to right): Drs. Donald R. Jasinski, Richard E. Belleville, Harris Isbell, William R. Martin, H. Frank Fraser, and Charles A. Haertzen.

Round Table Discussion

Measurement of Subjective Responses to Psychoactive Drugs and Personality Characteristics of Narcotic Addicts

(Drs. Isbell, Fraser, Belleville, Haertzen, Jasinski, and Martin)

Dr. Isbell:

I believe that I mentioned to you this morning we were markedly impressed when we studied methadone and subsequently other drugs with the subjective effects they produced and also with observable changes in behavior. This is something Dr. Himmelsbach hadn't provided us tools for measuring, so we had to devise our own. Dr. Fraser has talked about this. However, we reached a point in time where I felt that we needed a much more sophisticated way of measuring subjective changes. I thought it would be a very simple task which my psychologists could complete in a few months in their spare time. I went to Dr. Hill and asked him to construct an inventory for measuring subjective effects of drugs which (1) could be administered repeatedly over a period of time so we could follow time action aspects of the drug effects, and (2) to distinguish between different types of drugs. I wanted to distinguish morphine from pentobarbital, LSD from marihuana, etc., and (3) I wanted it in a hurry. I needed to have it in 3 or 4 months. Dr. Hill assigned this task to Dick Belleville, and after he had worked on it for a few years, bequeathed it to Chuck Haertzen, who is still working on it. They have achieved what I asked them to do, except that I don't understand it. So, I think with that I am going to leave its description to Dick Belleville.

Dr. Belleville:

Let me express my regret, first of all, that Harris Hill wasn't able to be with us this afternoon since it was his persistence, perserverance and patience that enabled us to carry off many of these early projects. The request by Dr. Isbell followed some much earlier attempts to measure the psychological effects of drugs using techniques that were available at that time, such as the Rorschach, the Bender Gestalt and the Draw-a-Person-Test. None of them seemed to be very useful for this purpose. There was a great deal of variability in responses and we were in no way able to predict or really measure accurately the effects of drugs. I think it was during the LSD studies that Dr. Isbell mentioned this morning that we added the MMPI to our battery. This gave us some rather encouraging results.

The MMPI profiles seemed somewhat consistent with the clinical observations of patients under the influence of drugs. This suggested that we might be able to develop methods for measuring subtle effects of drugs in an addict population. The technique we adopted for developing our item pool was the sentence completion test. Subjects were instructed to complete the remainder of a sentence which began with a phrase such as "if only." The subjects were presented with an array of incomplete sentences under the different drug conditions. After careful selection and editing, these completed sentences became the bulk of the items finally adopted. We assembled approximately 3,300 such items into an inventory; this was eventually reduced to 550 items. The task seemed deceptively simple, initially, but as it evolved there were difficulties in establishing valid external criteria against which to measure the effects of the drugs. We also ran into the difficulty of heavy scale overlap and attributed these to the common drug effects. At this point, Chuck Haertzen took over the project and introduced more sophisticated techniques for item analysis and scale development.

Dr. Haertzen:

One of the reasons for the long delay in delivering scales was that we continued to administer the ARCI to more and more subjects. Originally we did an item analysis after we had run about 30 subjects under a drug condition and with some conditions such as LSD we got quite a few significant effects as compared with placebo, but with some other drugs such as pyrahexyl we didn't obtain very many. We gradually increased the number of subjects and each time we increased our N, the number of significant items increased. We still have not probably reached the level of significance which can be achieved, even after accumulating 100 subjects under certain drug conditions. The other factor in the final analysis was the feeling that perhaps scales developed by some of the traditional methods were not altogether satisfactory. One of the typical criticisms of the scales developed for the MMPI for any clinical group is that some scales probably weren't too effective because they measured general attributes of maladjustment. To rectify an analogous problem in the measurement of subject drug effects, I became interested in developing some pattern scales. These, I believe, are more effective scales because general drug effects are eliminated. Dr. Martin has at times made me uncomfortable with the items excluded by this procedure as in the case of marihuana. Some scales (e.g., Marihuana Scale) have been refined to the degree that they do not measure some important subjective changes. There has to be some kind of balance perhaps between the empiric scales which give you the type of item that samples characteristic subjective drug effects produced by a particular drug and the pattern or group scales which have the greater power to differentiate drugs.

Dr. Isbell:

Many of the scales that Dr. Haertzen has developed have been used very effectively by Drs. Jasinski and Martin. They do give dose response curves so, Don, will you continue the discussion.

Dr. Jasinski:

Early studies by Dr. Isbell and then Dr. Wikler of subjective states produced by narcotic antagonists were based essentially on subject interviews. Dr. Martin studied cyclazocine and nalorphine using the single dose questionnaire and identified symptom and sign syndromes that distinguished these drugs from morphinelike agents. Dr. Martin asked Dr. Haertzen to study the subjective effects of cyclazocine and nalorphine with the ARCI. Dr. Haertzen demonstrated that the sedative and the "psychotomimetic" effects of cyclazocine and nalorphine were measurable using items of the PCAG and LSD scales. After some preliminary studies by Drs. McClane and Martin using subscales of the ARCI, we began exploiting the ARCI using subscales of the MBG, PCAG, and LSD scales in classifying nalorphinelike and morphinelike drugs.

Dr. Isbell:

So after 25 years, we got my little project of a few weeks finished. Dr. Martin, do you want to say anything about this?

Dr. Martin:

I really think that Frank Fraser ought to tell a little bit about the development of the single-dose and the chronic-dose questionnaires because he and Dr. Isbell didn't wait for Dr. Haertzen, Dr. Belleville, or Dr. Hill to develop their questionnaires.

Dr. Isbell:

We couldn't.

Dr. Martin:

The single-dose questionnaire proved to be a remarkably simple and powerful instrument.

Dr. Fraser:

First of all, I would also like to pay tribute to Harris Hill who unfortunately could not be with us today. Harris Hill would come up with a solution to your problem. He is a phenomenal man. As an example, he taught me that one of the strong points of an ordinal scale was that you have a middle point. That had never occurred to me. Dr. Hill made many contributions to the single-dose and chronic-dose questionnaires. Dr. Martin also contributed to the scoring and validation of these scales. Single-dose questionnaires have been very helpful in obtaining the addict's attitude toward drugs. As I pointed out this morning, the addict in identifying dope seems to be able to even predict the degree of physical dependence. The correlation between identification of dope and physical dependence for seven drugs and a placebo was 0.98. This is really phenomenal. I think we should also recognize contributions of the addicts for the manner in which they cooperated in describing the effects of drugs.

Dr. Martin:

A little earlier, Dr. Wikler was rightly critical of efforts measuring the subjective effects of drugs using questionnaires. To a degree, those of us who participated in the development and application of these scales didn't trust them either. We, therefore, made vigorous efforts to validate these methods. We have found that scale scores covary with physiologic changes across time, that relative potency estimates between drugs using scale scores and physiologic measures agree and that the potency estimates further agree for estimates of analgesic potency in nonaddict prisoners.

Dr. Isbell:

Well, our time is beginning to grow short, and I would like to turn away from subjective effects of drugs to the personality characteristics of narcotic addicts. This subject must be limited fairly sharply because we have only 4 minutes left. You have heard today from Dr. Felix and from Chuck Haertzen and so on about the pervasiveness of psychopathy, whatever psychopathy may be. This is suggestive that whatever psychopathy is, if it is anything, it may be a very important thing to work on. I wonder if Dr. Martin would care to be so brash as to comment.

Dr. Martin:

We have been recently developing the concept that the fundamental pathologic process in the addict may involve increased need states which may give rise in turn to increased egocentricity and impulsivity which in turn give rise to sociopathic and hypophoric feelings. Dr. Haertzen has assisted in the development of scales which may assist in the measurement of existing feelings of egocentricity or impulsivity, hypophoria, needs, and sociopathy.We feel that addicts, alcoholics, and others who have antisocial personalities may "want" more than other people and that many of their feelings of rejection, as well as their excessive narcissism, may stem from exaggerated and ungratified needs.

Round Table on Hospital Treatment Programs (Left to right): Drs. James F. Maddux, James V. Lowry, Victor H. Vogel, Robert W. Rasor, Dale C. Cameron, and Murray A. Diamond.

Round Table Discussion

Hospital Treatment Programs

(Drs. Vogel, Lowry, Diamond, Rasor, Maddux, and Cameron)

Dr. Vogel:

As I sit through these very fine research papers, I keep wondering whether we as clinicians have taken full advantage and have we been sensitive to some of the research that has been going on. Conversely, I wonder also whether researchers are sensitive to the needs of the clinicians who are treating patients. Certainly, there should be a better association, so we can fulfill one another's needs a little better. What are we doing for patients; what are we doing for addicts? This is primarily a research-oriented meeting, of course, however, it is also an opportunity to consider some of the research applications to clinical treatment. I was reminded by one thing that was said a few minutes ago, that the California program, which I was associated with for 5 or 6 years, had the legal requirement of a minimum of 6 months hospitalization or institutionalization before addicts were eligible for community parole. This was based on work that has been referred to here as physiological, indicating that biochemical remnants of addiction are left after withdrawal for that period of time. The California program administrators felt this time was unnecessarily long so it was shortened; now I think in the California program addicts are eligible for parole after a minimum of 3 months. I had planned to tell you something about the California Rehabilitation

Program, but as a good chairman I am going to surrender time and get on to the other panelists. I won't waste time in introductions of the people here. They are all well known to you, so we'll ask James Victor Lowry to share his reminiscences.

Dr. Lowry:

Thank you very much. Victor likes to use that name "Victor" because he's proud of it, and if it makes him feel better that's fine. I'm usually known as Jim. I spent two sessions at the Fort Worth Hospital, one when it opened, and two sessions at the Lexington Hospital, the last one between '54 and '57. From 1954 to 1957 was also a time of transition. During the first 10 years after the Hospital was opened, there were about 5,000 voluntary patients admitted. After World War II when addiction became more popular, particularly in the large cities, in the ghettos and among the black population, we had a tremendous increase in voluntary admissions so that in the second 10 years there were about 24,000 voluntary admissions to the Hospital. This made it possible to change the characteristics of the Hospital from a prison which it was because of its inheritance and the fact that it was spawned out of the Federal Bureau of Prisons and developed into something that was more akin to a hospital. There wasn't anything that could be done about the architecture, except to take down some of the bars or to jam up some of the locks so the grills couldn't be locked. But this change in the patient population allowed us to move toward an open hospital. The second thing that happened during this period was the institution of a system of administrative physicians where it was possible for one physician to follow a patient from the time he left the withdrawal service until he was discharged. It also made possible the doing away with another remnant of the prison type of approach and that was the so-called disciplinary board. If problems arose, they had to be settled by the patient's physician, the patient and other members of the staff. It also made possible the discontinuation of the use of the "hole" or "F Section" and I think everybody felt good about that. Vic mentioned the shortening of the length of stay. It was difficult to rationalize some of the lengths of stay of patients and for a while it was 6 months. We then decided the real test comes when a patient goes back to the community, so we reduced it to 4 months and asked them to come back at the end of 2 months. Very few of them came back, only those who were proud to prove that they had been able to stay off drugs. The other thing that happened during this time was we found out that a relatively few patients accounted for a great many admissions and that a very large number of patients were admitted to the Hospital only once. Probably the greatest contribution made at that time was that of the training program which was under the direction of Bob Rasor. I say this because I find graduates of the residency program of this Hospital scattered over the United States and doing important things in very many places. My present work takes me around the country and I see them and the excellent things they are doing. They always seem to be the persons in the medical community who are looked to for advice and consultation with regard to the care of the addict patient.

I was delighted to hear this morning that we finally got around to talking about drug addicts and drug addiction. I have always been a strong supporter of research on drugs and I certainly am happy that there have been drug addicts who have been research subjects. I was also delighted to hear this morning that there have been some studies about addicts as people and about addiction. I was also disappointed to learn that this most worthwhile activity had such a short life span. I would like to add my voice to the two that were raised this morning to encourage research in the field of sociology. I was pleased to be reminded again of the old system of classifying drug addicts. I have a little different one that I designed myself. I remember prewar addicts as being of a very specific type; they were con men, professional criminals, and card dealers, I learned more from them than almost anybody I've been acquainted with in my lifetime. I found their lessons very useful, whether I was dealing with the Congress or State Legislature, or anybody else in my consultation work. After the war, we saw the poor black ghetto addict and then in the 1960's we saw the "flower people" junkies. The "flower people" originally were not addicts but they became subjects for exploitation by drug peddlers. Unfortunately, there were drugs that were alleged to be mind expanding. It is too bad they weren't originally described as "mind boggling" because they attracted the flower people. Then we had the Aquarius junkies followed by the Nixon era of junkies, and these were characterized as being antiestablishment. If a drug was destructive, they wanted to use it to see whether it was really worth having. Lately, we've had the post-Watergate junkies who are different than the Nixon era junkies, and now we have a new group emerging called the pseudojunkies. The pseudojunkie is one who is full of needle marks and thinks he's an addict, but about half of the time he has no signs of physical dependence. We've heard a lot of discussion about characteristics of different drugs, and work that's been done with one drug with groups of addicts, but so far as real life is concerned, most of the addicts these days are great mixers, and they enjoy a variety of drugs, usually at the same time, and so I have a new category that I call the "tossed salad" junkie. They use whatever they can get at any time. Unfortunately, we're moving into, on the West Coast at least, a greater use of cocaine and amphetamine.

Probably the most used addicting drug that we have these days is alcohol, and while its abuse was not a reason for admission to the Hospital at Lexington and Fort Worth, I want to remind you that at least 20 percent of all psychiatric hospital admissions are because of overuse of alcohol. It is a problem of which I am becoming more aware. We see many, many depressions in the older age group, particularly the women, and they try to dissolve their depression by using alcohol. I am aware of some very nice work that was done here in research on alcohol, and I wonder why it was not continued. Is this because of the administrative divorce that occurred, or is it because other things are more attractive?

Dr. Vogel:

Your mention of pseudojunkies reminds me of one aspect of the California civil commitment program. While criminal charges are held in abeyance, the addict can be civilly committed for 7 years unless he earns his release from the program in the community in a shorter time. The result of this is that the criminal with a misdemeanor fights to keep out of the program because he would rather do a year in jail than have 7 years of supervision. The felons, on the other hand, who may not be addicts at all, with the assistance of their lawyers, try to get certified as addicts so they can get into the program, hoping to get out of the program soon as nonaddicts.

Next in order of MOC tenure is Dr. Diamond who is going to tell us something, I think, about not only the old Lexington program but what's going on in Louisiana.

Dr. Diamond:

It occurred to me that just rehashing or restating what one remembered isn't very productive, particularly since there isn't even a hospital to remember. I would like rather to talk about what actually goes on, in what Dr. Peterson called the "outside world." The community I'm in differs from California in that it is a no-program community, meaning the State really has no program. I guess they think they don't need one, or maybe they don't think they can afford one, or maybe they don't have the experts to run one; whatever, they just don't have one. The physicians of New Orleans are not too different from others. However, I'm not sure that in the southern tip of Louisiana they consider drug abuse an illness. In studying admissions to a large private general hospital with which I was associated, having recently re-retired, where they admit and discharge about 50 patients a day, over a year's period I found only four patients who had a diagnosis of drug abuse. To what degree this low incidence of drug problem is a consequence of the physician not recognizing or wishing to recognize that there was a relationship between the individual's present illness and drug use or abuse or the patient pressures not to have this stigmatizing diagnosis made cannot be assessed. A similar situation obtains in the Charity Hospital in New Orleans which has about 2,400 beds. Some patients with drug problems are probably diagnosed as psychoneurotic or psychotic. Still others who may be suspected of having drug problems may be discharged without a diagnosis and end up with a community physician or in a community mental health center. Thus, drug abusers are commonly ignored by most physicians.

As a practicing psychiatrist, I am seeing two types of drug abusers. The first is young patients 14 to 25 years old who are also having legal problems. Of those using heroin, only a few are addicted. We see more methadone addicts. This group of patients usually have been members of a methadone clinic program, having graduated or escaped, and are addicted to methadone. Methadone has become a street drug. A second more common population are young marihuana smokers who also use some LSD and cocaine. There are also older addicts. The comment was made "when you stopped you were older." There are some who don't stop and they're older and using drugs. It should not surprise you that there are addicts who are using drugs in abnormal and ill-advised fashion, who are 30, 40, and 50 years of age. They are around and live in the community. This is excluding those who are alcoholics who are 30, 40, and 50. There are also older people who are, in their terms, "addicted to barbiturates" or "addicted to morphine." The physicians maintain them and their addiction stays. Many of these patients are probably being admitted to hospitals and are being treated for other illnesses while being in one fashion or other withdrawn, and then continuing in private psychiatric facilities or mental health centers.

One of the other problems that physicians are contributing to is the overuse of minor tranquilizers. Valium and Librium are potentially habit forming. There have been a number of post-Valium convulsions noted in the city and in almost every hospital in the city, be it public or private. There is some concern about overprescription but as yet not enough concern to make people stop ordering it. Interestingly enough, patients themselves have hoped that physicians would expose them less to Valium but are perfectly willing to take the quick respites from their anxieties and from their depressions even though the rebound is as bad if not worse than the condition for which it was given.

There is an abounding area of knowledge which was developed at the Hospitals and ARC that somehow doesn't get to the outside world; it just doesn't get there.

Dr. Vogel:

Your reference to getting papers cleared reminded me of the time that I wrote a paper and sent it to the Surgeon General's Office for clearance, in which I referred to an epidemic of drug addiction. The word came back, "you can't say that drug addiction is an epidemic. Epidemics refer to infectious diseases." The next MOC in order at the Lexington Hospital is Bob Rasor.

Dr. Rasor:

Well, I think as most of you know I followed Murray at the Hospital in '62 and I think for some time after that the program went along pretty much as it had traditionally for a good many years. The admission rate was not quite as high as it had been before. The thing that I would like to concentrate on are the changes that took place in 1966 to 1969 when I left. Other people will have to comment on the changes after that. Certain legislation was passed that did change the Hospital drastically at that time and really led to the demise of the Hospital as we knew it. One of the changes was the passage of the Community Mental Health Centers Act in 1966 and this shifted federally funded psychiatric treatment to the community level. Another was the NARA legislation with which most of you are familiar. Further, the Public Health Service was reorganized and at that time the two Hospitals at Fort Worth and Lexington became a part of the National Institute of Mental Health and were designated as Clinical Research Centers. The mission was roughly to conduct clinical demonstration projects and research in the treatment of all phases of drug dependency. This changed the mission of the Hospital entirely. This didn't happen over night but was ongoing. The changes that took place were very drastic. One of the first things that happened was the elimination of the voluntary patients, and of course, this cut down the workload tremendously because as people who were at the Hospitals knew, the voluntary patients were the ones who kept coming and coming and coming. At one time we were admitting some 4,000 or 5,000 patients a year. Doctors on duty would sometimes admit something like 20 or 30 patients a day. I believe it was July 1967 that our first NARA patient was admitted. I think most of you are familiar with the NARA legislation that provided inpatient and outpatient care and I think somebody else will go into this legislation in more detail. NARA legislation also changed the Hospital. Some people referred to the Hospitals as hospitallike prisons; some prisonlike hospitals. There's no doubt they were designed for prisoner patients. The original legislation for these Hospitals was for them to take care of prisoner-patients who had violated laws. We were changing this institution from a prisonlike hospital to a rehabilitation center. Many of the prisoners had vocational assignments. At that time, some of us thought work could be therapeutic. We had prison industries, and I thought they were good prison industries. We had a prison farm, needletrades industry, clothing industry, and printing industry and all of these except the print shop were eventually phased out. We also had something like 30, 40, or 50 patients working in food services. We had patients working in sanitation and the laundry. As the prisoner population decreased, we didn't have a lot of help to take over these functions. Vic tells me I'm running out of time. The thing that I want to emphasize is the chaotic nature of this period. The physical changes came about much faster than the psychological changes of adjusting to the new mission of the Hospital. I think much of the chaos continued after I departed from the Hospital. But it was an interesting phase in the history of these institutions starting back in 1935 and proceeding to 1974.

Dr. Vogel:

We'll look forward to your printed paper. Speaking of chaos in admissions, I recall in the first days when the institution was opened 40 years ago the first addicts came in by the trainload from Fort Leavenworth. I was the only so-designated staff psychiatrist, and I'd never had any psychiatric training. I got along for a year until Mike Pescor and Bob Felix came along with some psychiatric training, and I felt immensely relieved.

Dr. Maddux was one of the MOC's at Fort Worth. He's going to tell us about a follow-up study there.

Dr. Maddux:

I feel honored to find myself in this distinguished company of investigators, clinicians, and program directors. I did time at Fort Worth twice and at Lexington once over the period from 1942 to 1969.With all of its talents and labor of over 40 years, the Addiction Research Center has not yet found a cure for chronic opioid addiction, and clinicians in the treatment programs have had to struggle along with a number of problems including insufficient and make-do theory and practices. I wanted to comment on one aspect of treatment. In a paper published in 1956 Dr. Lowry asserted that the institution could only begin treatment and the remainder of treatment must be accomplished in the community. Subsequently, Rasor and Diamond and others supported this assertion. Because the Fort Worth program always operated under somewhat less pressure and a smaller patient load, we were able in the early 1960's to develop several explorations in transitional and posthospital services for patients and to try to test their effectiveness. We developed a special prerelease program for term patients in which we gave them concentrated preparation for the kinds of problems they'd encountered when they left the institution. They were given practice in how to interview employers and how to get a driver's license. We had businessmen and others come in from the community to tell about what's expected by employers. We followed up a group of 50 of these patients who went through this program, and we also followed a group of 50 term patients who did not have this special prerelease program on posthospital aspects of drug use and employment. We couldn't find any difference in the two groups. Then with the help of an agency in Houston called the Vocational Rehabilitation Service we were able to get a half-way house in operation from 1965 through 1968 for patients from the Fort Worth Center. This half-way house seemed like a great idea, in that, when patients left the Hospital and were abruptly placed in the community, they didn't immediately have to find a place to live or a job. They could go into this nice residence and stay there and have group discussions about whatever problems they felt they were having. They were given help in finding jobs and getting into training and into education. The half-way house found itself in serious difficulty. The residents didn't want to pay any attention to the small number of regulations the house had. A few of the residents would encounter drug sellers on the streets and think that they might as well have a heroin fix since it was offered to them free by their friends. Then they'd have another one. We found that almost the entire household of 15 or 20 residents was using heroin, occasionally or daily. Almost all of the first residents were discharged in order to reestablish a drug-free environment inside the house. A follow-up study was done on the patients who went through the half-way house and on a comparison group. It wasn't a very good follow-up study because they didn't have enough money and resources and they lost a lot of the subjects. Again they found out there wasn't much difference in drug use, employment rates, or in institutionalization rates between the treated groups and the comparison group. We did another project which we called a continuum of services from 1966 to 1969 in which we had a very good, well-coordinated continuum of hospital and posthospital services between the Fort Worth Hospital and 14 community agencies in San Antonio. To make a long story short, when we did the 1-year follow-up of the group that had this continuum of services and of a comparison group who were discharged from the Fort Worth Center just before we set up the continuum of service program, we found very little difference between the groups in estimates of drug use, arrests, and employment. We found that about 10 percent of both the comparison subjects and the experimental subjects appeared to be free from heroin use throughout the first year after they left the Hospital. This is somewhat reminiscent of Pescor's study of 1943 in which he found that about 15 percent of the patients were reportedly abstinent at the time of his follow-up and that of Hunt and Odoroff, published in 1962, in which they found that 10 percent of the patients appeared not to become readdicted. The conclusion that I have come to is that providing a well-organized continuum of hospital and community services doesn't seem to make much difference. Further followup studies indicate that achievement of enduring cure is an unusual event. We might as well abandon the cult of cure and begin to think that opioid drug addiction like chronic hypertension and some idiopathic convulsive states, migraine headache and chronic schizophrenia are probably not curable, at least in our present state of knowledge. The best we can do is to provide some service to reduce dysfunction.

Dr. Vogel:

Perhaps we should take another look at conclusions about the California Rehabilitation Program and narcotic testing periodically, with the result that 18 percent of those released from the program remained drug free for 3 years with supervision and were thus discharged from the institution. We felt that intensive followup, small case load by the parole officer, and periodic testing were responsible for this to a large extent. Subsequently, because most relapses occurred in the first year, fewer in the second year, practically none in the third year, the law was changed reducing required drug-free parole from 3 to 2 years.

I think Dr. Dale Cameron was never MOC at the Lexington or Fort Worth Hospitals, but he was MOC at St. Elizabeths Hospital, and, of course, his international (WHO) experience makes him an extremely valuable panelist.

Dr. Cameron:

I should like to relate two brief personal anecdotes in order to help illustrate a point of view and something important that has been happening here at the Addiction Research Center in Lexington. Dr. Kolb earlier referred to a paper that I wrote, and which his father generously "marked up," and which I didn't publish right away. Let me tell you the end of that story. When I went to Fort Worth, it happened that the MOC was Dr. Ossenfort and his secretary was Mrs. Gladys Palmer. She had also served as secretary for Dr. Kolb, as well as several other PHS officers, and was to be my secretary. It fell to her lot to organize my files when I arrived at the Hospital. As she went through them, she found this heavily edited paper and came into my office and said "Dr. Cameron, did you ever publish this?" I said "No, I didn't." She said, "Why not?" I said because after rereading it two or three times I found every criticism valid, and being rather embarrassed thought I'd better wait a little while before revising it. She said, "Oh, Dr. Cameron, this has the fewest marks of any paper I have ever seen Dr. Kolb review." I said. "Gladys, you've got to be kidding." This simply illustrates that it took me quite a while as a young man to understand that Dr. Kolb wouldn't have been so critical in the best sense of the word unless he cared and that without caring he would not have taken the time. It was an example of his being a personal mentor, even to the junior officers under his purview. Let me note that I found myself at Fort Worth at a reasonably tender age, concerned with trying to help foster a program that would assist drug users who had not been notable for managing their own lives in a responsible fashion. The problem was to help them to learn to assume responsibility for their own actions, and to do this in an institution that tended to foster dependency since most of the decisions about the patients' daily living were made by the staff. This presented a dilemma: How to try to encourage independent and responsible action in a setting that tends to rob the individual of this opportunity. We devoted much of our time to trying to figure out how to give patients an opportunity to demonstrate responsibility and at the same time exercise our responsibility to society of maintaining them in a prison hospital. This was a very interesting kind of exercise and it has stood me in good stead the rest of my life; it is a basic problem in mental hospitals and in broader programs. I think it may be easier to do in some respects at the community level than in an institution.

Now a second anecdote. One Friday afternoon after Dr. Ossenfort, the Medical Officer in Charge, had been transferred, I found myself, the executive officer, as the medical officer in temporary charge. At about 2 o'clock in the afternoon, I received a call from Washington. It was Dr. Kolb. He said, "Dr. Cameron, we have decided that we are going to transfer 400 psychotic patients from St. Elizabeths Hospital to Fort Worth in order to make room in St. Elizabeths for Navy patients." This was during World War II. I might say this was a sudden addition to the mission of the hospital. He said, "Please figure out where you would house them, what additional materials and food supplies you will need, and what extra personnel will be required, both professional and nonprofessional, and let me know by Monday." I was 29. I called together the hospital department heads, and we went to work. By working hard over the weekend, we had our recommendations ready on Monday, as requested. You heard another part of this story from Bob Felix the other day when he talked about going to support a deficiency appropriation. Part of that deficiency grew out of the recommendations we submitted from Fort Worth. Something very significant happened. They didn't send anyone from Washington to "second guess" what would be needed at Fort Worth. Dr. Kolb took our recommendations at face value because they were jointly arrived at by the staff, and he provided what we said we needed. In other words, at the age of 29, I was given a major opportunity to assume responsibility for my own actions.

Now let me turn to yet another little anecdote. We did move in the patients from St. Elizabeths, and the first 200 came before the new MOC arrived. Later I had an opportunity to go to St. Elizabeths to help bring down another train load of 100. Among this 100 there was one prison car full of patients who were thought to be high escape risks. During the journey, we burned out a bearing on the prison car. I had to decide whether to wait some days for another prison car or to proceed with a standard pullman car. I reasoned that any man who could get a pullman window open was entitled to his freedom, and we proceeded without waiting for the prison car. Later, while on a siding in the Ozark Mountains, we lost a patient. He did get a pullman window open and we had to leave someone who knew him to see if he could be found. He was a very sick schizophrenic and it was some 3 or 4 days before he was located.

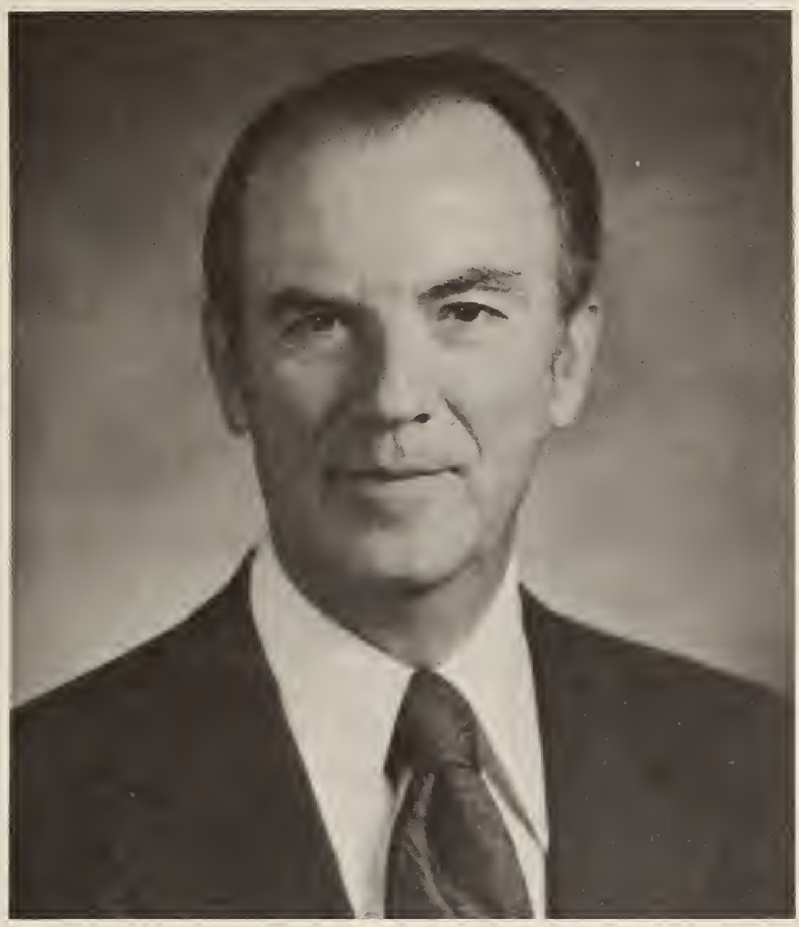
These anecdotes, I think, show that at a relatively early age, I among many others in the Service was given an opportunity to assume responsibility. This meeting is illustrative of that phenomenon. There are quite a number of persons here who were the key figures in the founding of an important program 40 years ago. They had to be young men at that time or they wouldn't be here today. The Service had a fairly rigorous mechanism for selecting personnel. It gave them rather close personal supervision from senior officers, and it gave the junior officers the opportunity to make their own mistakes. This is what has been happening at the Addiction Research Center. This, I think, is one of the reasons why it has prospered and flourished; there is a lesson in it for continuing operation of research and treatment programs.

Dr. Vogel:

Thank you, Dale. Yes, I was 30 years old when I became the "chief psychiatrist" at the new hospital in Fort Worth. We were transferred away from Fort Worth when our middle son was 2 weeks old. We carried him in a basket. This was a result of a phone call from Dr. Kolb. "If you can get to Johns Hopkins by the time school opens next Monday, we'll stake you to a year's postgraduate study." So we made the train. Dr. DuPont was quoted in the California press recently as saying, I think probably at a Congressional hearing, that the solution to the addiction problem is to provide addicts with an alternative way of life. That's what we've been trying to do for years, and that's what we should continue to do. That's the nub of the whole problem, isn't it? Thank you very much.

Dr. Lawrence C. Kolb, Sr., *at his desk at the Lexington facility on May 25, 1935, opening day*

Dr. Lawrence C. Kolb, Sr., *(left), presents a gavel to Steve Featherstone, a member of the Lexington Chamber of Commerce, on the 20th anniversary of the Hospital. Dr. C.K. Himmelsbach and Mr. W.K. McCurry (right) look on. Mr. Featherstone was a friend and supporter of the Hospital.*



Dr. James F. Maddux, *Medical Officer in Charge, U.S. Public Health Service Hospital, Fort Worth, 1962–69*

History of the Hospital Treatment Programs, 1935–74

James F. Maddux, M.D.

Throughout most of their existence, the two Public Health Service Hospitals located at Lexington, Ky., and Fort Worth, Tex., served as the principal resources in the United States for treatment of drug dependence of the morphine type. The Lexington hospital was opened in May, 1935, and was closed in February, 1974. The Fort Worth hospital served for a somewhat shorter period, from November 1938, to October 1971. From opening to closure the two hospitals admitted over 60,000 drug-dependent patients; because many patients were readmitted, the total admissions exceeded 100,000. The treatment programs changed from beginning to end, as they responded to new treatment concepts, to accumulating clinical experience, and to outside social and legal events.

Habitual use of a morphinelike drug has been called the opium disease, the opium habit, morphinism, morphinomania, narcotic addiction, opiate addiction, opioid addiction, and drug dependence of the morphine type. With loss of consistency but gain of authenticity I use different terms as they were used by writers in different periods of history.

Treatment Before the Public Health Service Hospitals

The comprehensive report by Terry and Pellens [67] provides much detail about treatment concepts and practices to 1928. When habitual use of opium or morphine became a noteworthy problem in the United States in the latter half of the 19th century, physicians debated whether to consider it a vice or a disease. The debate continued into the 20th century. In 1918, in response to a questionnaire, 425 health officials stated that physicians in their communities considered it a disease, while 542 reported that physicians regarded it as a vice [67, p. 154].

Regular use was most frequently attributed to relief of pain from chronic physical conditions such as rheumatism, neuralgia, sciatica, "female complaints," renal colic, asthma, and others. Mental and emotional strain were cited as causes of the opium habit, but not as frequently as physical conditions. In the 19th century physicians knew that regular use led to craving and to withdrawal symptoms.

Before the Public Health Service Hospitals opened, treatment of narcotic addiction was focused almost exclusively on the early abstinence syndrome. Physicians debated the merits and hazards of abrupt withdrawal, rapid withdrawal, and slow withdrawal. They used many different substances to treat early abstinence: chloral hydrate, sodium bromide, alcohol, paraldehyde, caffeine, cocaine, and cannabis. They used purgatives, including calomel and castor oil, apparently justified by the belief that the drug addiction "toxemia" came partly from intestinal intoxication. Intoxication with belladonna or belladonna drugs, scopolamine or atropine, was advocated and used. After reviewing the treatments in use, Terry and Pellens [67, p. 627] commented:

> The various methods described in general indicate that the basis of the majority of them is merely the separation of the patient from the drug.

Although not reported in the medical literature as a "treatment" for narcotic addiction, many physicians maintained the drug dependence of their patients by regularly prescribing or dispensing morphine. The legality of this practice became uncertain after the Harrison Narcotic Act was approved in 1914. In 1919 the Treasury Department established a regulation, supported by subsequent U.S. Supreme Court decisions, which prohibited prescribing of narcotics for an addict to maintain his customary use. Nearly all physicians then ceased maintaining narcotic addiction, and alarm was expressed for the welfare of addicts suddenly deprived of drugs. Somewhat paradoxically, in view of the new regulation, approximately 44 clinics which dispensed narcotic drugs to addicts were set up in various cities [62]. The first clinics were opened in 1919. Controversy surrounded them. Advocates claimed that the addicts were able to give up criminal activities and to obtain employment; opponents claimed that the drugs were diverted to other persons and that crime and drug traffic increased. Unfortunately no data were collected to permit evaluation of the claimed benefits and detriments. All the clinics were closed by the end of 1923.

Deprived of their drug supplies from both physicians and the narcotic clinics, some addicts stopped using, but many turned to illegal sources of drugs. They were arrested and convicted of law violation, and they accumulated in Federal prisons. By 1928, narcotic drug law violators constituted about one-third of the populations of the penitentiaries at Atlanta, Leavenworth, and McNeil Island [6]. Nearly all of these prisoners had been addicted to narcotic drugs.

During this period of heightened controversy, the Public Health Service assigned Dr. Lawrence Kolb to study the addiction problem. From 1923 to 1928 Kolb conducted epidemiologic and clinical studies. He obtained detailed life histories of 230 chronic opiate users. He found that 86 percent of his drug users had been affected with "nervous instability" before they became addicted [33]. He identified three factors which prompted chronic drug use and relapse after a period of abstinence [34]:

(1) A primary psychic factor. This factor prompted the original addiction and relapse after abstinence.
(2) Physical dependence. Kolb felt that this factor became more important with increasing years of addiction. Some of his subjects addicted 10 years or more reported feelings of lassitude and undue fatigue which lasted 6 to 9 months after cure.
(3) Memory association and habit. The repeated relief of discomfort by taking morphine or heroin formed a strong association between physical and mental distress and the taking of the drug.

The accumulation of narcotic drug users in the Federal prisons prompted the Superintendent of Prisons, James V. Bennett, to propose that special Federal institutions be established for treatment and rehabilitation of the addicts. In 1928 Congressman Stephen G. Porter introduced a bill to establish two narcotic farms for addicts. Although the Public Health Service had shown concern about addiction as a public health problem, the agency did not seek the proposed institutions. At the hearings the Surgeon General indicated that the Public Health Service did not desire to initiate support for this enterprise [71]. Nonetheless the bill to establish two institutions for persons addicted to narcotic drugs was passed by the Congress and signed by the President on January 19, 1929 (Public Law 70–672).

The Early Years: 1935 Through 1949

The act set forth the purpose of the institutions and conditions of treatment as follows:

> An Act to establish two United States narcotic farms for the confinement and treatment of persons addicted to the use of habit-forming narcotic drugs who have been convicted of offenses against the United States and for other purposes. . .
>
> The term "addict" means any person who habitually uses any habit-forming narcotic drug as defined in this act so as to endanger public morals, health, safety, or welfare, or who is or has been so far addicted to the use of such habit-forming drugs as to have lost the power of self-control with reference to his addiction . . . treatment of persons admitted shall be designed to rehabilitate them, restore them to health, and where necessary train them to be self-supporting and self-reliant.
>
> That any person, except an unconvicted alien, addicted to the use of habit-forming drugs . . . may apply to the Secretary of the Treasury or his authorized representative, for admission . . . . No such addict shall be admitted unless he voluntarily submits to treatment for the maximum amount of time estimated by the Surgeon General . . . as necessary to effect a cure . . . if any addict voluntarily submits himself to treatment he may be confined in a United States narcotic farm for a period not exceeding the amount of time estimated by the Surgeon General as necessary to effect a cure . . . the record of his voluntary commitment shall be confidential and not divulged.

An interdepartmental committee composed of the Attorney General, the Secretary of the Treasury, and the Secretary of War chose the sites for the two narcotic farms. The site at Lexington, Ky., included approximately 1,050 acres located 5 miles west of the city. The site at Fort Worth, Tex., included approximately 1,400 acres located 7 miles southeast of the city. The Lexington facility consisted of several multistory buildings connected by corridors and tunnels, and was designed to accommodate approximately 1,200 patients. A separate building for women patients was completed in 1941. As may be seen in figures 1 and 2, the Fort Worth facility had buildings more dispersed than those at Lexington; it was designed to accommodate approximately 1,000 patients. Both institutions had farms and dairies, as was customary for

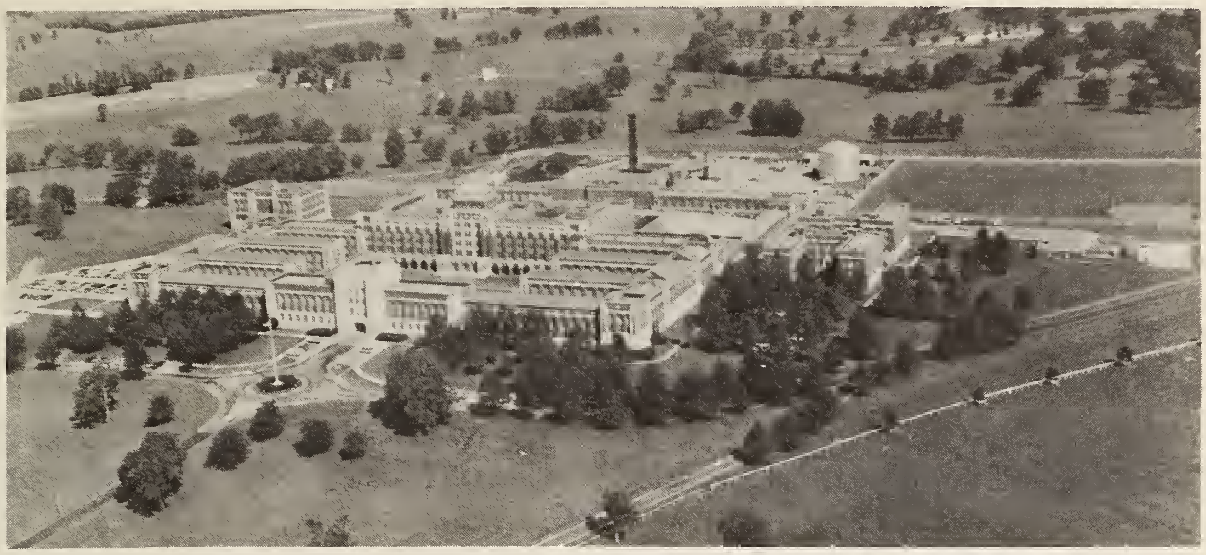


FIGURE 1. *The U.S. Public Health Service Hospital, Lexington, Ky.*

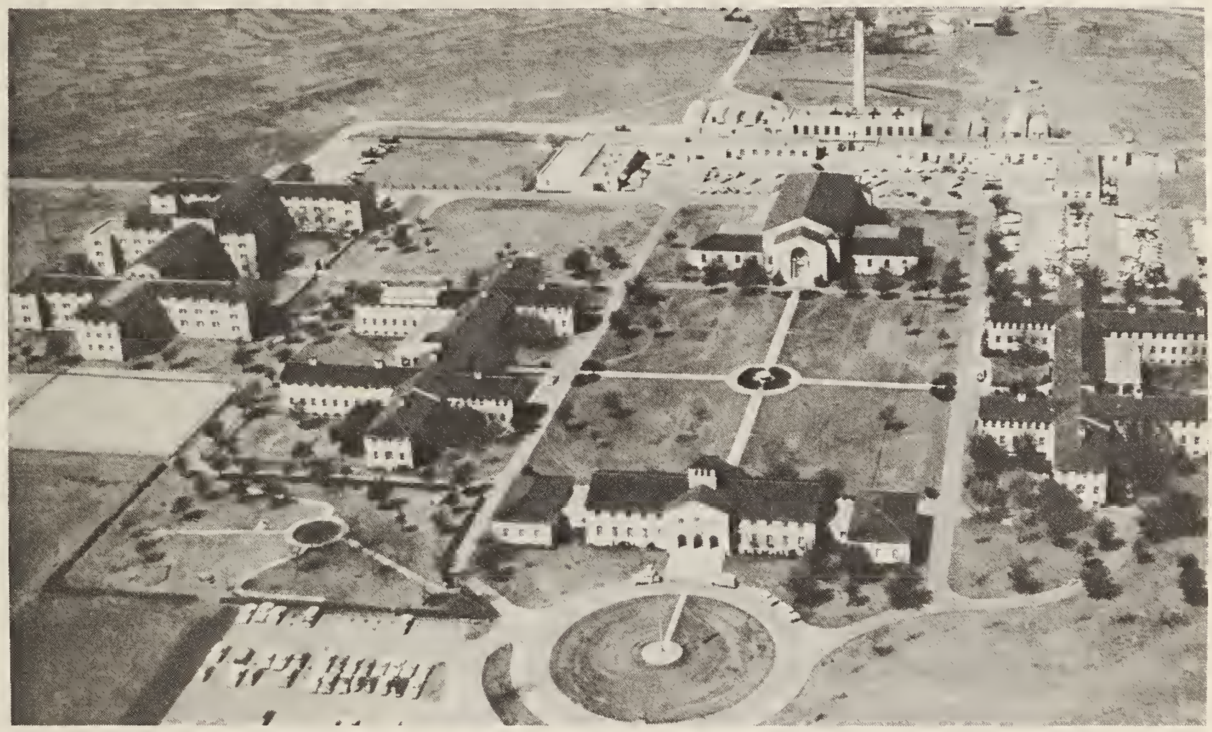


FIGURE 2. *The U.S. Public Health Service Hospital, Fort Worth, Tex.*

mental institutions at that time. Most persons have considered the buildings attractive and the grounds beautiful. Because the hospitals would care for Federal prisoners, bars and grilles were located at most windows and in corridors.

When the Lexington institution was opened in May, 1935, it was called the "U.S. Narcotic Farm." A year later its name was changed to "U.S. Public Health Service Hospital." When the Fort Worth institution was opened in November, 1938, it was from the beginning called "U.S. Public Health Service Hospital."

The treatment programs of the two hospitals represented pioneering advances. Not only the abstinence syndrome, but also the more important mental and emotional problems were to be treated. In 1939 Kolb [35], who served as the first Medical Officer in Charge at Lexington, commented:

> The hospitals' approach to the treatment problem is based on the assumption that, while physical addiction is a very important thing that must be cured, the psychological angles of the case are much more important, and on the belief that if the patient is to achieve permanent cure he must be relieved of his emotional difficulties or taught to adjust to them without resort to narcotics.

Kolb and associates [35–37] described four fairly distinct elements of the hospital treatment program: drug withdrawal, drug-free environment, psychotherapy, and controlled activities.

1. *Drug withdrawal.* In 1938, after reviewing the withdrawal treatments frequently used at that time, they concluded that tolerance and physical dependence are self-limited and disappear when the opium is withdrawn, regardless of treatment. They described the procedure, developed by Himmelsbach, for objectively measuring the intensity of abstinence, and they reported the rapid withdrawal procedure developed at the Lexington hospital. After signs of abstinence appeared, they gave small doses of morphine or codeine, reducing the dosage on succeeding days, and terminating the drug in 14 days or less. Warm baths and small doses of sedatives were provided if needed. They found that about 80 percent of the addicts had mild habits, and required only codeine for withdrawal.

2. *Drug-free environment.* Residence in a drug-free environment was considered important to permit recovery from physical dependence, which might require several months. Kolb [35] also believed that by being compelled to adjust for several months without narcotics, the patient became unconditioned to his drug-use habit.

3. *Psychotherapy.* All patients received some "psychotherapy" in the form of encouragement and persuasion. "Intensive psychotherapy" was reportedly attempted with some patients, but the theoretical orientation and techniques of the psychotherapy were not described.

4. *Controlled activities.* The staff members supervised and controlled all the activities of patients. Patients were assigned to work on the farm, in maintenance, and in shops. Athletic programs and other recreational activities were provided. Breaking of rules brought disciplinary action, consisting of loss of a privilege or more severe penalty. Loss of "good time" (time earned by prisoners for good behavior which reduced the required period of institutional confinement) was frequently applied. With the exception of loss of good time, prisoner and voluntary patients came under the same disciplinary procedures. They attempted to make the discipline therapeutic. Kolb and Ossenfort asserted [37]:

> The approach to the disciplinary cases is dominated throughout by the viewpoint of the psychiatrist, and punishment for violation of rules plays no part in the scheme.

Each voluntary patient signed a statement that he would stay until cured, and staff members initially assumed that the law authorized them to hold the patient even if he decided to leave. But in March 1936, a U.S. District Court in Kentucky decided that voluntary patients could not be held against their will. The first annual report of the Lexington hospital stated that treatment of voluntary patients had not been very effective because most of them left before treatment was completed. In succeeding years approximately 70 percent of the voluntary patients signed out against medical advice [59]. For most patients, staff members recommended a hospital stay of 4 to 6 months for recovery from the physical dependence and a start at learning to live without drugs. In 1946 the "Blue Grass" admission was initiated [32]. The Commonwealth of Kentucky made habitual narcotic drug use a misdemeanor, with punishment of up to 1 year in jail. Patients who left against advice were readmitted only if they pleaded guilty to narcotic drug use in a local Kentucky court. The consequent sentence was then suspended on condition the person stay at the Lexington hospital until treatment was completed.

After the Fort Worth Hospital opened in November 1938, male patients residing west of the Mississippi River usually went to that hospital, while male patients residing east of the Mississippi River usually went to the Lexington Hospital. Women were not admitted to either hospital until 1941, when a separate building for women was completed at the Lexington Hospital. Women from all parts of the United States were sent to the Lexington Hospital, except that during a 5-year period, 1947–52, 109 women addicts were admitted to the Fort Worth Hospital.

Pescor [56] reported a statistical description of 1,036 male patients admitted to the Lexington Hospital during fiscal year 1936–37. Most (88 percent) were white; 9 percent were black; 3 percent fell into other racial groups. They had a median of 8 years of school. They first became addicted at the mean age of 28; they were admitted to the hospital at the mean age of 39. Thirty-three percent had never married. The mean age at first arrest was 28; three-fourths had no delinquency record prior to addiction. At the time of admission, 51 percent reported morphine as the last drug used, 43 percent reported heroin, and 6 percent reported other drugs.

Clinical observation during the 1940's confirmed Kolb's finding of personality difficulties among most addicts. In 1944, Felix [17] reported that, with the exception of a small group of normal individuals accidentally addicted, the mental problems of addicts could be classified in the categories of psychoneurosis, psychopathic personality, and psychosis. He considered drug addiction a symptom of personality difficulty.

In 1943 Pescor [57] reported the first followup study of addicts treated at the Lexington Hospital. He attempted to get followup information on 4,766 male patients discharged during the years 1936 through 1940. In this remarkable study, Pescor encountered several methodological problems, the major one consisting of failure to get followup information on over one-third of the patients. He reported the followup addiction status of his patients as follows: unknown—40 percent; dead—7 percent; relapsed—40 percent; abstinent—13 percent. Paroled prisoners had a higher percentage (31 percent) abstinent than other groups.

In 1947 and 1948 Isbell and associates [27, 28] reported that methadone had pharmacological effects closely resembling but longer acting than those of morphine, and that it could be smoothly substituted for morphine in physically dependent persons. In 1948 Vogel, Isbell, and Chapman [73] described their initial experience in treating early abstinence by substitution and withdrawal of methadone. The abstinence syndrome from methadone seemed milder than that from morphine or heroin. First administered subcutaneously, the methadone was later administered orally. Methdone substitution has since become the standard procedure for withdrawal throughout the United States.

During World War II a pressing need developed for additional facilities to treat mentally ill personnel of the expanding U.S. Navy. In 1942 President Roosevelt signed an executive order making the two hospitals available for treatment of mentally ill persons from the Navy, Marine Corps, and Coast Guard. Simultaneously the prevalence of addiction in the United States apparently declined, probably because controls on shipping reduced illicit smuggling, and the warring powers bought all the available opium [26]. As shown in table 1 and figure 3, annual admissions of addicts to the two hospitals increased from 1935 through 1942, and then decreased during the years of 1943 through 1945.

During the war years, the patient population at the Fort Worth Hospital came to consist mainly of nonaddict mentally ill persons. In addition to mentally ill persons from the Navy, Marine Corps, and Coast Guard, the hospital admitted several hundred mentally ill merchant seamen and others eligible for medical care from the Public Health Service by transfer from Saint Elizabeths Hospital in Washington, D.C. This was done to make beds available at Saint Elizabeths Hospital for care of mentally ill Navy personnel. The addict population at the Lexington Hospital declined, reaching a low point of approximately 800 in 1946. During and following World War II the Lexington Hospital also cared for nonaddict mentally ill persons, but the census of these patients never exceeded 150.

During the early years, 1935 through 1949, the two hospitals served as

TABLE 1

Admissions to the Public Health Service Hospitals at Lexington and Fort Worth, 1935–73. Data for 1935–65 were taken from Ball et al. [4, 5]. Data for 1969–73 were provided by the Drug Abuse Epidemiology Data Center, Institute of Behavioral Research, Texas Christian University.

Year	First admissions	Readmissions	Total
1935	821	2	823
1936	963	55	1018
1937	680	150	830
1938	1069	247	1316
1939	1204	289	1493
1940	1522	428	1950
1941	1197	777	1974
1942	1333	863	2196
1943	1040	957	1997
1944	847	825	1672
1945	772	830	1602
1946	943	998	1941
1947	1396	1548	2944
1948	1321	1397	2718
1949	1913	1962	3875
1950	2725	1808	4533
1951	2569	1579	4148
1952	2223	2267	4490
1953	2677	1818	4495
1954	2269	1560	3829
1955	2289	1632	3921
1956	2337	1928	4265
1957	2244	1845	4089
1958	2340	1907	4247
1959	2219	1943	4162
1960	2493	1651	4144
1961	1980	1450	3430
1962	1875	1533	3408
1963	1750	1361	3111
1964	1911	1277	3188
1965			2646
1966			
1967	Data not available		
1968			
1969	2479	343	2822
1970	2520	496	3016
1971	1497	256	1753
1972	705	133	838
1973	264	60	324

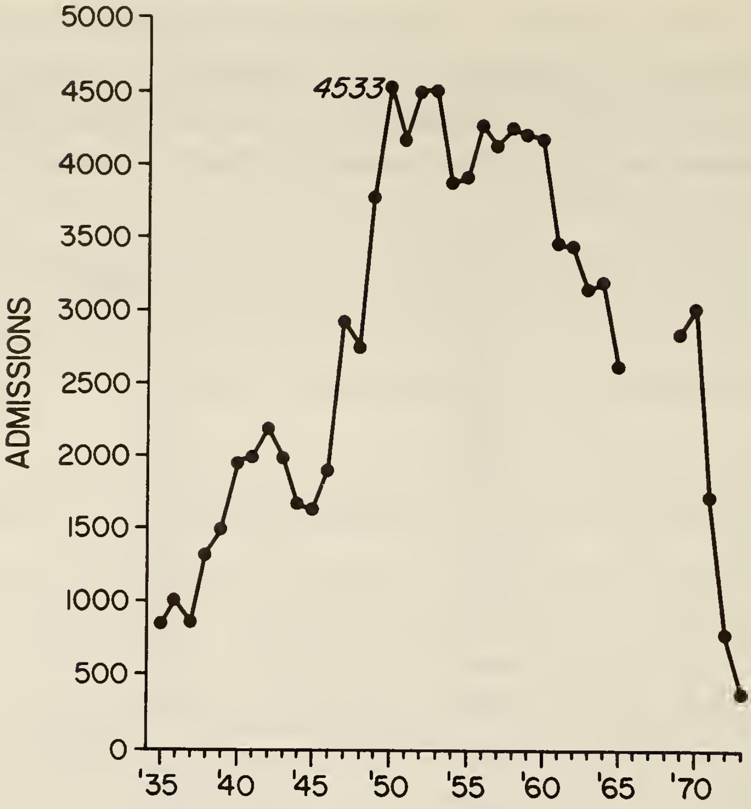


FIGURE 3. *Admissions, by year, of drug-dependent patients to the Lexington and Fort Worth hospitals, 1935–73.*

almost the only treatment resources for treatment of narcotic addiction in the United States. Because of ethical and legal prohibitions, physicians retreated from treatment of addiction. General hospitals refused to admit addicts for treatment of addiction. Apparently it was widely assumed that the two Federal hospitals would treat all addicts in the United States.

In 1948 the research division of the Lexington Hospital was administratively separated from the Lexington Hospital, given a new name, the Addiction Research Center, and made part of the newly established National Institute of Mental Health (NIMH). The new designation, the stable and expanded financial support from the NIMH, and the fortunate acquisition and retention of talented research leaders opened a long period, continuing to the present time, of outstanding psychopharmacological research. The work of the Addiction Research Center is summarized in other chapters of this book.

Until the Addiction Research Center was established and separated from the Lexington Hospital, research on addiction was considered an important mission of both hospitals, and many of the professional staff conducted clinical and treatment investigations. With loss of their research mission, the two hospitals were transferred from the NIMH to the Bureau of Medical Services, in which the medical care functions of the Public Health Service were concentrated. The hospitals were then staffed and financed for their medical care mission. Research was never prohibited; the professional staff member with research interests simply had to find time for research after his clinical work was done. Furthermore, in the late 1940's the number of admissions increased, making greater demand for clinical service to patients.

The Middle Years: 1950 Through 1966

The increase in addict admissions noted in the late 1940's continued into the 1950's, reflecting increased prevalence of heroin addiction in the United States. The mean of annual admissions to both hospitals increased from 2,287 during the decade 1940–49 to 4,218 during the decade 1950–59. In 1950 the annual admissions numbered 4,533, the highest number of all years. Increased voluntary admissions accounted for the increased total admissions; admissions of prisoners declined somewhat during the 1950's and remained about level during early 1960's. The Lexington Hospital nearly always had a waiting list of voluntary applicants; the Fort Worth Hospital rarely had a waiting list. The average daily census of addict patients at Lexington during the 1950's was approximately 1,200; at Fort Worth, approximately 350. Although most admissions were voluntary, most of the addict patients in both hospitals at any time were prisoners because they stayed longer than the voluntary patients.

During the early 1960's the number of admissions to the hospitals decreased a moderate amount. The mean of annual admissions during the 5-year period 1960–64 was 3,456. In 1965 the annual admissions dropped to 2,646. The reduced admissions probably resulted from the establishment of State and local treatment programs, especially in New York and California, to which users of morphinelike drugs were admitted who would otherwise have come to Lexington or Fort Worth.

The addict patient census at the Lexington Hospital dropped from approximately 1,200 during the 1950's to approximately 1,000 during the early 1960's. The addict census at the Fort Worth Hospital continued at approximately 350 during the early 1960's. As the addict census at the Fort Worth Hospital increased following World War II, the 600 beds allocated for mentally ill veterans were reduced. In 1965 the Fort Worth Hospital had an average daily census of 360 addict patients, 174 veterans, and 176 merchant seamen and others, making a total census of 710 patients.

The two hospitals became overcrowded because of increased admissions, but also because more space was used by increased professional staff, and for expanded remedial education, vocational training, and activity therapies. Study of the hospitals in the 1960's led to a revised patient capacity of 1,042 for the Lexington Hospital and 777 for the Fort Worth Hospital.

The characteristics of patients changed. In 1937 [56], 9 percent of the men patients admitted were black; in 1962 [3], 30 percent were black. The percentage of persons classified as Mexican-American or Puerto Rican increased from 1 percent in 1937 to 16 percent in 1962. In 1937 the mean age of men patients at the time of admission was 39; in 1962, 34. Men patients admitted in 1937 to the Lexington hospital reported their first drug use at a median age of 26 (estimated from Pescor's grouped data); men patients admitted in 1965 reported first opiate use at a median age of 20 [5]. In 1937 three-fourths of the patients had no delinquency record prior to addiction; in 1965, arrest commonly preceded first use of opiates. Highest rates of admission shifted from the southern States to northern States with large metropolitan centers. In 1963, 44 percent of the men patients came from New York and Illinois [4].

Heroin replaced morphine as the drug most commonly used at the time of admission. Barbiturate dependence became a problem. In 1964 Hamburger [22] reported that 23 percent of 1,000 narcotic addicts admitted to the Lexington Hospital had physical dependence on a barbiturate drug.

The "psychic factor" which, Kolb believed, prompted the narcotic use at the time of the initial addiction and at relapse was described and elaborated in the clinical reports from the two hospitals during the 1950's and the 1960's. In 1953 Wikler and Rasor [79] identified three overlapping formulations of the psychiatric aspects of addiction: (1) A symptomatological formulation, in which the drugs are used primarily to relieve symptoms of pain, anxiety, and depression; (2) a psychoanalytic formulation, in which elements of orality and narcissism lead to feelings of frustration, hostility, or depression which are relieved by the drugs; (3) a pharmacodynamic formulation, in which the self-perpetuating character of opiate drug use is directly related to the pharmacologic properties of these agents.

The Addiction Research Center did not conduct treatment research, but some of the research had important implications for treatment. From clinical observations and animal studies beginning in the 1940's, Wikler and associates [75–78] carried out a long series of complicated experiments with rats to determine the importance of classical and operant conditioning in relapse to opioid-seeking behavior. He demonstrated classical conditioning of abstinence phenomena, but he found, surprisingly, that previous morphine addiction alone had sufficient potence in prompting relapse to obscure any possible effects of previous conditioning, either classical or operant [77]. Although the hospital staff members assumed, or hoped, that the hospital milieu provided a corrective experience from which the patient would acquire habits of living to replace the drug-using habit, they did not describe the treatment in the terminology of conditioning theory. Martin and associates [49, 50, 52] studied protracted abstinence, and suggested use of narcotic antagonists in treatment. The evidence of protracted abstinence supported the standard clinical practice of recommending 4 to 6 months in a controlled drug-free environment for recovery from the physical dependence.

Reflecting a psychiatric trend of that time, psychodynamic concepts derived from psychoanalysis began to appear in descriptions of the patients and in their treatment. In 1956 Lowry [41] referred to failure of emotional maturation in the addicts related to absence of any constant person with whom identification could occur. Lewis and Osberg [40] found evidence of oral deprivation; in addition to the usual intrapsychic defense mechanisms, they identified and described the interpersonal defense mechanisms of manipulation, corruption, and wedging utilized by the patients. Maddux [43] described the hospital milieu as designed to facilitate ego growth.

In 1953 Fraser and Grider [19] first called attention to the limited applicability of individual psychotherapy for many patients. They commented:

> Many addicts deny any need of psychiatric assistance and many frankly refuse therapy. The drug addict has found something—morphine—which allays his vague free-floating anxiety. To demand of him that he relinquish a tested product for the relatively unpredictable success of psychotherapy is to demand more than many addicts can give.

In 1958 Rasor [58] reported that only 28 patients were receiving individual psychotherapy at the Lexington Hospital; at that time the hospital had a patient population of over 1,000. Eight years later, at the Fort Worth Hospital, Maddux [44] commented:

> Most do not eagerly and effectively use conventional psychotherapy or social casework . . .

Group therapy began at the Fort Worth Hospital in 1950 [29] and at the Lexington Hospital in 1951 [68]. Lowry [41] stated that group therapy appeared more suitable than individual psychotherapy for patients with personality trait or sociopathic disturbances, and Maddux [42] observed that patients in the group challenge and confront each other with their evasions, denials, and manipulations. Prompted partly by the Synanon procedure [80, 81], patient-led small group discussions were initiated at the Fort Worth Hospital in 1963. By 1966, three-fourths of the addict patients at the Fort Worth Hospital were in group counseling; nearly all of these groups were led by employees.

During the early 1960's, sociotherapy received special emphasis at the

Fort Worth Hospital [8, 43]. The staff attempted to make the social milieu stable, firm, and orderly; every employee in contact with patients was conceived as having a therapeutic role. Symptomatic behavior, especially disruptive or antisocial action, was blocked. All staff members were encouraged to acknowledge the consequent anger or tension, and to try to improve the patient's "outsight," that is, his understanding of his social environment.

Studies at the Fort Worth hospital by Blachly and associates [9], and by Tittle and Tittle [69, 70] indicated that the patients learned from peers to adhere to the "prison code." This prisoner value system was associated with a negative attitude toward treatment. During a 2-year period, 1964–66, Hughes and associates [23] manipulated the social structure on a unit for 30 prisoner-patients to develop procedures to reduce adherence to the prison code, and to produce a rehabilitation-oriented community. They found several useful procedures: withholding of staff discipline for deviant behavior of an individual while giving his peers opportunity to change his behavior; working with any natural group, especially the hometown clique; dividing the patients into small self-help interaction groups which met three times a week with group leaders who in turn met weekly with the professional treatment team; inviting peers to contribute to the periodic conferences of professional staff on progress of individuals; and permitting only rehabilitation-oriented patients to hold office with significant power in the unit self-government. Hughes and his associates were continuously involved in practically all the activities on the unit. They believed that the prison code was effectively undermined, and that the new social organization became a major vehicle for therapeutic change.

The problem of premature departure against medical advice of most voluntary patients continued. The Blue Grass procedure was used to some extent at the Lexington hospital, but it had the disadvantage that patients were required to obtain a criminal conviction as a condition of admission. It was discontinued about 1956. Levine and Monroe [39] reported that 74 percent of voluntary patients admitted during 1960 and 1961 left against medical advice. Of those who remained to complete hospital treatment, most had the legal pressure of probation or suspension of sentence from a State court.

In addition to the problem of voluntary patients who left too soon, a new problem developed of prisoner-patients who stayed too long. Due to alarm about the apparent marked increase of narcotic addiction in the United States, Congress enacted the Narcotics Control Act of 1956 (Public Law 84–728), which increased the penalties for narcotic law violations, prescribed mandatory minimum penalties, and prohibited probation or parole for certain offenses. In consequence, many prisoner-patients accumulated in the Lexington and Fort Worth hospitals who could not be released on parole when it seemed appropriate. In 1962, 38 percent of the prisoners in the two hospitals had sentences of 5 years or longer and were not eligible for parole [42].

Many of the drug users had erratic or no-work records. Many had not learned to work under supervision, to cooperate with others, to take care of tools and equipment, and to persist in a task to completion. Consequently work therapy, or "training in work habits," was considered an important component of treatment. Throughout the entire history of both hospitals, nearly every addict patient who was considered physically able to work had a job. On innumerable occasions work supervisors and other staff members patiently and firmly responded to work behavior such as the following:

> A patient receiving on-the-job training from an electrician was asked to obtain from the storeroom a conduit of a specified diameter. The patient quickly obtained the conduit. The electrician asked if the conduit was the required diameter. The patient said it was. The electrician asked if he measured it. "It looked about the right size," said the patient. "Measure it," said the electrician. On measuring it, the patient found that the conduit was not the specified size. The electrician explained the importance of precision in their work. The patient returned to the storeroom and obtained the correct size.
>
> A patient sweeping the floor of the dining hall left behind some debris. The supervisor showed him the debris and asked him to sweep that portion of the floor again. The patient threw down the broom and exclaimed, "If you want it swept, sweep it yourself!" The patient persisted in his refusal to sweep that portion of the floor again. He was removed from his job, deprived of privileges, and counseled about the conventional relationship of an employee to his supervisor. His work performance in the hospital subsequently became satisfactory.

In addition to unstable work performance, many of the drug users had limited vocational skills. Most had worked only as semiskilled or unskilled laborers. Many of the work assignments in the hospitals offered opportunities for training in skilled trades. These assignments were formalized into apprentice training; patients received certificates for satisfactory completion of training. Classroom instruction was provided in trade-related theory and practice. Although most patients did not show interest or persistence in developing saleable trade skills, some persisted, and after discharge obtained employment in skilled occupations which they learned while in the hospital [1, 2]. One patient received training in the hospital in X-ray technology, and after discharge obtained a job as an X-ray technician. Another patient trained in maintenance mechanics obtained employment in this occupation. Another trained in dental technology obtained a job as a dental technician. Another learned sign painting in the hospital, and after discharge worked in this occupation. Agricultural training came to have less importance in producing saleable job skills, and the farms were closed. The Fort Worth farm was closed in 1961 and the Lexington farm in 1967.

Three features of the job assignments of patients became subjects of controversy among staff. First, the work of patients was interrupted when they went to other activities such as individual or group psychotherapy or counseling, social casework conferences, progress evaluation conferences, ward meetings, dental appointments, and others. Real work was expected of patients, and the hospitals depended partly upon patient workers. Frequent, extended, and unanticipated absences of patient-workers from their jobs created problems for work supervisors. Controversy over this problem never disappeared, but communication and joint planning among the work supervisors, the other therapists, and the clinical administrators kept the problem at a tolerable level most of the time.

Second, employees and outsiders at times expressed their opinion that the hospitals "exploited" patients by requiring them to work in areas important to hospital operations such as the food service, the laundry, the janitorial service, and physical maintenance. The patients quickly learned to manipulate any feelings of guilt or anxiety among employees about job assignments in these areas.

Third, pay for work was advocated. Advocates of pay felt that, even though patients received needed training in work habits and in trade skills, and they could be fairly expected to help in institution work, monetary compensation might improve incentive and performance. Small "pay" of a sort was provided to workers in the capital fund industries. These "industries" were self-supporting units authorized by law, and included the farms, printing, and shops for manufacture of furniture and clothing. Workers who maintained established production standards were "paid" in cigarettes. In 1964 the cigarette pay was discontinued at the Fort Worth hospital and in lieu of the cigarette award, a cash award of $2.00 per month was begun. This cash "payment" for satisfactory work performance was extended to all the job assignments in the hospital.

Educational deficits also restricted the employment potential of patients. Of 3,398 patients admitted to both hospitals in 1962, 67 percent had failed to complete high school [43]. At the Fort Worth hospital approximately 10 percent of the addicts were found functionally illiterate. Remedial education became an important component of the hospital programs. Baganz and Maddux [2] found that a small number of patients who obtained high school equivalency certificates while hospitalized were employed more frequently than others 1 year after discharge.

Security always represented an element of the hospital treatment programs. The security tasks included custody of Federal prisoners, maintaining a drug-free environment, and maintaining a safe and orderly environment for patients and staff. Custody of prisoners did not require special emphasis. Escape attempts occurred infrequently, perhaps partly because prisoners considered to be escape artists were transferred to prisons. Although both hospitals were constructed with bars and grilles, they were about equivalent in physical security to minimum custody prisons. Constant effort was required to maintain a drug-free environment, for one or more patients, or relatives, or friends of patients, were often attempting to bring illicit drugs into the hospitals. On a few occasions, employees who felt sorry for patients brought morphinelike or other psychoactive drugs into the hospitals for them. Illicit drugs became available to patients only occasionally and in small amounts; nearly always the hospital environment remained free of illicit drugs.

Patients lived under several grades of supervision from close to minimum. Most patients had freedom of movement within the buildings and on the outside grounds. Violence occasionally erupted. Patients had fights in which they attacked each other with table knives, screw drivers, or other makeshift weapons. The fights usually occurred as sudden explosions of anger, rarely as planned assaults. The occasional group fights had antagonist groups usually formed on a racial, ethnic, or geographic basis. The addict patients did not attack employees. The only serious assault on an employee came from a nonaddict patient. In a tragic event at Lexington in 1962, a former nonaddict patient entered the home on the reservation of the Medical Officer in Charge, Dr. Robert W. Rasor, and shot him, his wife, and an addict patient working in his home. Mrs. Rasor was paralyzed by the wound and died 6 years later.

Security and treatment activities were conducted in uneasy balance. Some of the professional staff members came into conflict with security officers, or resented security procedures which they felt interfered with treatment. The hospital administrators attempted to avoid excessive regimentation on the one hand, and anarchy on the other. They probably achieved as good a balance as was possible most of the time. With the advent of sociotherapy, previously mentioned, many professional staff members came to view security not as antithetical to treatment, but as an element of treatment.

Most of the professional staff involved in therapeutic interaction with patients found the experience more difficult, frustrating, and stressful than their work with psychotic or psychoneurotic patients who did not use morphinelike drugs [30]. In clinical reports the addict patients were described as impulsive, impatient, self-centered, and demanding. They seemed to have low tolerance for pain or discomfort from any source.

They attempted to manipulate, to wedge, and to corrupt. They exploited conflicts among staff members about problems of discipline, work, and security. Excessive and prolonged tension in professional staff members sometimes led to withdrawal from patients or attack upon the institution. Some withdrew from all but minimum interaction with patients. Others became intense partisans of the patients and on their behalf attacked the institution, its staff, its organization, and its procedures.

When the hospitals were opened, aftercare was recognized as desirable but it could not be given as a regular part of the treatment. The law provided only for institutional care. Only patients who left on probation or parole received regular posthospital supervision. During the 1950's the need for aftercare was frequently emphasized. Lowry [41] perhaps expressed the need most strongly:

> Hospital treatment can start a patient on the way to recovery, but it cannot provide a lifelong immunity that protects the patient against relapse. Hospital treatment can initiate rehabilitation, but it must be completed after the patient returns to the community.

The frequency of readmission of previously treated patients, and followup studies showing a high rate of relapse to drug use made posthospital service seem more urgent. Approximately 36 percent of all admissions during the first 20 years, 1935–55, were readmissions. Pescor's study in 1943 [57] indicated that 40 percent or more relapsed to drug use after discharge. Hunt and Odoroff [24] reported that 90 percent of 1,881 patients discharged from the Lexington hospital to New York City in the 1950's became readdicted during a 4½-year followup period.

From 1957 through 1961 the NIMH conducted a demonstration program in New York City which provided counseling and referral to community agencies of addict patients returning to New York City from the Lexington hospital [11]. The program staff saw 912 discharged patients. Only a small number of the patients followed through on referrals. Employment was found for many patients, but they seldom stayed on a job more than a few weeks. The service did not seem to affect the patients very much. Quantitative outcome data to estimate the effects of the program were not obtained.

Following this exploratory project in New York City, the Fort Worth hospital conducted three projects of transitional and posthospital service in which controlled evaluation of results was attempted. First, a 30-day prerelease program primarily for prisoner-patients was established to prepare them for the immediate problems they would encounter on return to the community. During the first 6 months after discharge, 50 patients who completed the program did no better on estimates of employment and voluntary abstinence than 50 patients discharged before the prerelease program began [47].

Second, the Fort Worth hospital assisted the Vocational Guidance Service in Houston to plan and develop a halfway house for addicts discharged to Houston from the Fort Worth hospital or from prisons [74]. During 4 years the halfway house admitted 113 former heroin users; 67 percent of the residents admitted were discharged for adverse behavior in the halfway house or were removed by legal intervention. Followup data on 86 percent of the residents and 40 percent of a comparison group indicated that the residents and the comparison subjects became readdicted in approximately the same proportions.

Third, the Fort Worth hospital and 14 community agencies in San Antonio provided a coordinated continuum of hospital and community agency services during 2½ years, July 1966 through December 1968 [45]. This project extended beyond the period called the Middle Years, 1950 through 1966, but it was planned and started during the Middle Years, and is more conveniently described in this part of the history of the hospitals. The project brought many more of morphinelike drug users into treatment: annual admissions from San Antonio during the first year of the project approximately tripled those of previous years. One-year followup information was obtained for 95 percent of 137 control patients discharged to San Antonio without special posthospital service, and for 87 percent of 111 experimental patients who were offered the comprehensive continuum of services. On estimates of posthospital voluntary abstinence and employment, the experimental subjects did no better than the control subjects.

All of these aftercare projects had a small number of "successful" patients who used the services provided, remained abstinent, and coped adequately with their problems. Extraordinary difficulty is encountered in getting complete, precise, and reliable followup data on addict patients, and the outcome data require cautious interpretation. Nonetheless the clinical experience and the results of these projects all pointed to the conclusion that hospitalization with aftercare for voluntary patients did not bring marked improvement over hospitalization alone. The limited effects of posthospital service did not seem to arise from deficits in quality or quantity of service offered; they seemed to come primarily from the impulsive, unsteady, and erratic behavior of most of the patients. Most patients did not use the services provided.

Somewhat reminiscent of the 1920's, the 1950's saw increased alarm and controversy in the United States on account of the apparent increasing illicit use of heroin, as well as increasing nonmedical use of sedative, stimulant, and hallucinogenic drugs. Increased penalties for narcotic violations with intensified law enforcement were both advocated and deplored. In addition to Kentucky, other States enacted laws which made addiction itself a crime. A California law of this type was declared unconstitutional in 1962 [64].

As I have noted, during the Early Years from 1935 through 1949, the Lexington and Fort Worth hospitals worked practically alone in treatment of drug dependence. During the Middle Years, 1950 through 1966, some State and local services were developed, and notable treatment innovations were introduced. The two Public Health Service hospitals did not work in as extreme isolation as during the early years. Nonetheless the new developments were geographically restricted to small portions of the United States and heavy clinical demand on the two hospitals continued.

New York City operated Riverside Hospital, a 141-bed facility for treatment of juvenile addicts, from 1952 into 1961. This hospital was closed after a followup study showed that only 8 (3 percent) of 247 former patients had not returned to the use of drugs at the time of followup [72]. Also in the 1950's three clinics for drug addicts were established in Chicago. In 1958 the exaddict self-help organization, Synanon, was established in California [80, 81].

Interest in compulsory treatment under civil commitment gained impetus. Although many States had laws which permitted involuntary civil commitment of narcotic addicts, these laws had been rarely used. In California in 1961, and in New York in 1962, legislation was enacted which led to the development of large rehabilitation programs based on civil commitment of the narcotic addicts.

Narcotic maintenance was revived. In 1955 the New York Academy of Medicine proposed the establishment of clinics in which narcotic drugs would be dispensed to addicts, with efforts to persuade them to undergo treatment [61]. In 1964, amid intense controversy, Dole and Nyswander began at the Rockefeller Institute (later Rockefeller University) in New York City to maintain a small number of heroin addicts on single daily oral doses of methadone. They reported that the daily methadone relieved narcotic hunger, that the patients ceased, except on rare occasions, to use heroin, and that the patients performed well in school and at various jobs [13]. This initial favorable experience formed the basis on which methadone maintenance subsequently became widespread throughout the United States.

Following the White House Conference on Narcotic and Drug Abuse in 1962, President Kennedy appointed an Advisory Commission on Narcotic and Drug Abuse to recommend a program to prevent drug abuse and to rehabilitate habitual drug misusers [18]. Among the 25 recommendations of the Commission, recommendations number 19, number 23, and number 25 had great importance for the two hospitals:

> 19. The Commission recommends that the Federal Government

encourage and increase assistance to States and municipalities to develop and strengthen their own treatment programs and confine its activities in the immediate future to research.

23. The Commission recommends that the Public Health Service Hospitals in Lexington, Ky., and Fort Worth, Tex., accept voluntary patients only for the purposes of research study in the future.
25. The Commission recommends that a Federal civil commitment statute be enacted to provide an alternative method of handling the federally convicted offender who is a confirmed narcotic or marihuana abuser.

On the basis of these recommendations, the Public Health Service planned to convert the two hospitals into clinical research centers. But before the research mission could be implemented, an important new clinical mission was assigned to the two hospitals.

In 1966 Congress enacted the Narcotic Addict Rehabilitation Act (Public Law 89–793), which provided for civil commitment of narcotic addicts by U.S. Courts for institutional treatment and aftercare. This law had great promise, for it seemed to solve three problems of treatment which had existed for many years: (1) premature departure from treatment by voluntary patients, (2) excessively prolonged institutional confinement of prisoners, and (3) lack of aftercare.

The Later Years: 1967–74

On January 1, 1967, the two hospitals were transferred from the Bureau of Medical Services to the National Institute of Mental Health. Each was renamed "National Institute of Mental Health Clinical Research Center," and each was assigned a new role of model treatment, training, and research center.

Treatment under the Narcotic Addict Rehabilitation Act (NARA) was implemented in 1967. The Act authorized the Surgeon General to enter into contracts with any public or private agency or person to provide examination or treatment of committed addicts, but, in order to develop the NARA program quickly, it was decided to use the Lexington and Fort Worth Centers in the early stages for the examination, evaluation, and institutional treatment. The Act consisted of four titles.

Title I authorized civil commitment for treatment of eligible addicts charged with a Federal offense who chose to be committed instead of prosecuted. Examination of the individual was required prior to commitment to determine if he was an addict who was likely to be rehabilitated. Addicts considered suitable for rehabilitation could then be committed to the Surgeon General for 36 months of institutional treatment and supervised aftercare.

Title II authorized civil commitment of eligible addicts convicted of a Federal offense. As in title I, examination was required prior to commitment to determine if the individual was an addict who was likely to be rehabilitated. Addicts considered suitable could then be committed to the Attorney General for a indeterminate period not to exceed 10 years of institutional treatment and supervised aftercare.

Title III authorized civil commitment of addicts not charged with any criminal offense. Any addict or related individual could petition the U. S. Attorney in the District in which he resided for treatment. If the person appeared to be an addict, and appropriate State or local treatment facilities were not available, the U.S. District Court could commit the person to custody of the Surgeon General for treatment. As in title I and title II, examination was required prior to commitment to determine if the person was an addict who was likely to be rehabilitated. Addicts considered suitable could then be committed to treatment in a hospital for a period not to exceed 6 months. Following hospital treatment of the addict, the court could, considering recommendations of the Surgeon General, place the person under custody of the Surgeon General for posthospital treatment for 36 months. During this period the person could be recommitted for 6 months of hospital care.

Title IV authorized financial assistance to States and localities for treatment centers for narcotic addicts. Grants to States and communities for treatment of addicts were later administered under the Community Mental Health Centers Act by amendments in 1968 (Public Law 90–574), in 1970 (Public Law 91–211), and in 1972 (Public Law 92–255).

For the two hospitals, now designated Clinical Research Centers, the NARA program required new clinical and administrative activities: examination and evaluation of patients for courts prior to commitment; transportation for patients between courts and the Centers; reports to courts; training of personnel for NARA field offices; and communication and cooperation with community agencies providing posthospital care under contract. Considering the large number of court officials, NIMH headquarters staff, Center staff, NARA field staff, and personnel of contract agencies who had to coordinate their activities in complicated procedures, the NARA program began quickly and effectively. The NARA was approved by Congress in November 1966; the first NARA patient was admitted to the Fort Worth Center in June, 1967. Admission of Federal prisoners to both Centers was discontinued in August, 1967. Admission of voluntary patients was discontinued at the Fort Worth Center in March 1968; and at Lexington Center in November 1968. Admission of veterans to the Fort Worth Center ceased in March 1968, and the veteran patients were transferred to facilities of the Veterans Administration.

During 1967 through 1973, 10,153 NARA patients were admitted to the two Centers. Of these 5 percent were committed under title I, 2 percent under title II and 93 percent under title III. Title II patients were admitted to the Lexington and Fort Worth Centers until August 1968, by which time the Bureau of Prisons had developed rehabilitation programs into which it could accept NARA patients. Women made up 15 percent of the total admissions. Before 1970 the admission information obtained with respect to ethnic background of NARA patients did not include categories for Puerto Rican or Mexican-American background. These categories were included in the information obtained in 1970 and subsequent years. The 5,931 NARA patients admitted during the years 1970 through 1973 had the following ethnic distribution: Anglo 43 percent; black 47 percent; Puerto Rican 1 percent; Mexican-American 9 percent.

Many of the NARA patients sent by courts to the Centers for examination and evaluation were found not suitable for treatment. Through 1968 the Fort Worth Center found 38 percent of the NARA admissions not suitable for treatment. Through 1971, the Lexington Center found a higher percentage, 51 percent, not suitable for treatment. Practically all of these persons were found to be narcotic addicts, but they were considered too antagonistic or disruptive to participate in the institution treatment program. Many entered the NARA program under title III as a consequence of legal pressure from a State court in lieu of prosecution for criminal charges, or as a condition of probation after conviction. Having entered the NARA program, these persons had complied in many instances with the State legal coercion, and some then acted to get themselves ejected from the NARA program. They refused to get out of bed; they would not come to interviews; they remained silent in group therapy; they refused to shower; they attempted to corrupt other patients; some threatened violence against staff or other patients. Staff members worked hard to draw these patients into therapeutic interaction before they reported them as not suitable for treatment.

During the first 2 years of the NARA program, 1967 and 1968, officials of U.S. Courts and staff members of community agencies became puzzled or dismayed by the large number of patients found not suitable for treatment. A heroin user would tell the judge that he strongly desired treatment in the NARA program; the judge would send him for examination to one of the Centers; there he would insist that he did not want treatment and intended to resume heroin use as soon as possible, and for about 3 weeks he would refuse to take part in the treatment program; when returned to the court as "not suitable," he would tell the judge that he did not understand why the staff of the Center rejected him, for he strongly desired treatment in the NARA program.

Thus many NARA patients who previously would have entered the

Centers voluntarily and signed out against advice now avoided commitment by adverse conduct. Furthermore, some patients committed for 6 months of institutional care under title III became so antagonistic during hospitalization that they were discharged and the court commitment was terminated. A study by Mandell and Amsel [48] showed that of 7,353 NARA patients admitted for examination from July 1, 1967 through June 3, 1971, only 35 percent were discharged to aftercare. The attrition continued after discharge to aftercare. Langenauer and Bowden [38] followed 252 title I and title III men discharged from the Lexington Center during the period July 1968 through June 1969. Only 97 (38 percent) of the 252 remained in aftercare during the sixth month after discharge. Patients were lost from aftercare in different ways: recommitment for institutional care, conviction and incarceration, death, and disappearance.

The NARA provided penalties for escape from institutional commitment under title III, but late in 1967 the U.S. District Court in Lexington determined that criminal prosecution for escape would be unconstitutional. Under this ruling the two Centers had no legal power to confine title III patients involuntarily, and aftercare agencies had no legal power to require that patients stay in aftercare. The Title III program became almost equivalent to a voluntary program. Nonetheless, only 10 percent of 5,859 NARA patients admitted to the Lexington Center through August 1971, walked away from the Center without authorization [12]. This low rate of escape probably occurred because the patients did not need to escape when they wanted to leave; they simply obtained a discharge as not suitable for treatment.

Gold and Chatham [20] studied 1,050 patients in aftercare during June 1971. On the basis of self-reports and urine tests, 46 percent used an illegal drug during that month. The authors did not report how many used an illegal drug during the entire period in aftercare. They reported that 52 percent were working full-time or part-time during the month studied. Langenauer and Bowden [38] reported that 86 percent of 97 patients remaining in aftercare in the sixth month had used an opioid drug at some time during the 6 months. Stephens and Cottrell [66] followed 200 NARA men patients discharged from the Lexington Center. They found that 87 percent used narcotics at some time during the first 6 months, but only 65 percent became readdicted. Thus, with respect to total abstinence, the NARA program did not seem to produce results markedly better than previous voluntary hospitalization alone or voluntary hospitalization with aftercare. The compulsory supervision may have somewhat reduced the amount and frequency of morphinelike drug use.

Although neither the NIMH nor the Department of Health, Education, and Welfare (DHEW) made any announcement, rumors that the

Fort Worth Center would be closed began in December 1967. In support of the rumors, the DHEW withdrew funds allocated for modernization of the buildings, and reduced funds for personnel. Simultaneously, funds were allocated to the Lexington Center for building modernization and for increased personnel. Officials of Federal, State, and local government agencies came to study the facility at Fort Worth for its possible use as a juvenile detention center, a junior college, or as a State mental hospital. They apparently knew, but the staff did not know, that the institution would be closed. While continuing to provide clinical care to NARA patients and others, the Fort Worth Center had over 3 difficult and confusing years while nonpublic plans to close the Center were made and reversed. Special pressure existed in 1969 in the headquarters of the DHEW to close the Center because of need to reduce the number of employees in the DHEW. Members of Congress objected to closure at that time on grounds of insufficient State and local facilities for treatment of drug users. This objection came to have less strength as State and local services expanded with contract and grant funds provided under title IV of the NARA and amendments to the Community Mental Health Services Act. The Fort Worth Center was closed in October 1971, 33 years after it was opened. NARA patients were subsequently sent to the Lexington Center or to contract facilities for examination and evaluation and inpatient care.

The buildings and grounds were transferred to the Department of Justice, and the facility was immediately converted into a Federal Correctional Institution (FCI) under the Bureau of Prisons. The new Fort Worth FCI provided confinement and rehabilitation services for prisoner addicts, for addicts committed under title II of the NARA, and for other special groups of Federal prisoners.

Meanwhile, changes were made at the Lexington Center. Conrad [12] described the new program. The interior of the buildings was modernized, and virtually all of the bars and grilles were removed. Physical seclusion was no longer used; the ultimate disciplinary sanction became expulsion from the program. Personnel was increased, and the patient census was reduced to approximately 500. In order to maintain a drug-free environment without rigid security procedures, the Center initiated random urine testing of all patients.

Treatment was carried out in five relatively autonomous therapeutic communities. With more staff and fewer patients, therapeutic interaction with patients became more intense. The major technique was that of confronting the patient with his past and present irresponsible behavior. The peer group of more advanced patients pressed the addict to make a commitment to change. The commitment to change was sought in concrete terms, and a detailed description of behavior to be changed was outlined by the staff and the peer group. While confrontation and behavior shaping were emphasized, the underlying dysphoria also required attention. Conrad stated:

> While the focus was on behavior, thoughts and feelings were also examined and dealt with, especially the widespread dysphoric feelings which emerge as the addict gets involved in treatment. The management of the depression which becomes evident in the addict as he gets engaged in treatment is a very difficult clinical problem, and one that seems to become more manifest the longer the addict remains in treatment.

One of the therapeutic communities, called Matrix House, was operated exclusively by ex-addicts, with two psychiatrists available as consultants. This unit was located in a separate building. Patients applied voluntarily for admission to Matrix House. Like Synanon, the community was run in an authoritarian style, but with an atmosphere of warmth and friendliness. Group confrontation sessions called "games" were conducted three evenings each week. The individual began in Matrix House with menial work and few privileges. Rewards and status were awarded on the basis of demonstrated responsible behavior. The Matrix House program was designed to last 18 months; during the later months the individual moved freely between the institution and the city of Lexington. As in other therapeutic communities with voluntary participation, most of the residents left before completing the program. Unfortunately, toward the end of the second year of operation, the ex-addict leaders of Matrix House violated the trust placed on them by the staff of the Center. They became involved in alleged antisocial activity which led to criminal charges against several of the leaders. The unit was terminated in 1972.

As the patient load was reduced the Center began to develop its research role. By 1970, research sections in psychology, neurology, social science, and experimental treatment had been developed.

All of the admissions shown in table 1 for the years 1969 through 1973 entered under the NARA. A peak of 3,016 NARA admissions occurred in 1970, and thereafter the number of annual admissions decreased markedly. During 1973 the Lexington Center had only 324 admissions. The decrease resulted from two conditions. First, more community facilities were awarded contracts to provide examination and evaluation and inpatient care for NARA patients, thereby reducing the number that would have gone to the Lexington Center. Second, under the legislation already mentioned, large and unprecedented sums of money were appropriated by Congress and granted to States and communities for services to addicts and drug abusers. This not only led progressively to less need for NARA commitment, it also began to make NARA III commitment illegal, for the U.S. Attorney could petition for commitment only if "appropriate State or other facilities are not available to such person . . . ." Partly because of the reduction of NARA commitments, administration of the NARA program was transferred from NIMH headquarters to the Lexington Center in 1972.

With loss of NARA patients, the Lexington Center became more vulnerable to pressure on and within the DHEW to reduce the number of Federal employees. The Lexington Center was closed in February 1974, nearly 39 years after it was opened. The NARA patients were thereafter cared for in contract facilities.

As with the Fort Worth facility, the institution was transferred to the Bureau of Prisons and immediately converted into a Federal Correctional Institution. The new Lexington FCI, like the Fort Worth FCI, began to serve prisoner-addicts, addicts committed under title II of NARA, and other special groups of Federal prisoners.

Treatment After Closure of the Hospitals

In 1975, 1 year after closure of the Lexington Center, the availability and variety of treatment services in the United States for persons dependent upon morphinelike drugs or other psychoactive drugs have radically changed from 1935, the year of its opening. From practically no special community services for drug users in 1935, extensive and widely distributed special services exist in 1975. The latest available national directory of drug abuse programs, published in 1972, listed 974 programs distributed throughout all the States [54]. In 1974 the community drug abuse treatment programs had an estimated combined capacity to treat 160,000 patients at any one time [15]. Federal leadership and financial assistance stimulated this growth of services. Federal support for the treatment and rehabilitation of drug users increased from $18 million in fiscal year 1967, the first year in which funds were appropriated under the NARA, to $241 million in fiscal year 1975 [16]. In 1971 President Nixon established the Special Action Office for Drug Abuse Prevention (SAODAP) to coordinate the work of 14 Federal agencies engaged in drug abuse prevention. Conceived as a temporary agency, the SAODAP is being phased out in 1975, and many of its coordinating functions are being assumed by the National Institute on Drug Abuse (NIDA). The NIDA was established in 1973 to serve as the principal Federal agency to conduct and promote treatment, prevention, research, education, and training in the field of drug abuse.

Current community treatment services are utilized primarily by the users of morphinelike drugs, principally heroin. Three basic treatment modalities are provided in most of the programs: methadone maintenance, detoxification, and drug-free treatment.

With the advent of methadone maintenance, an historical cycle was completed. The clinics of 1919–23 maintained dependence by providing morphine to addicts until they were closed in a wave of medical and public condemnation. In the opinion of the American Medical Association, narcotic maintenance then became unethical except in unusual circumstances, and it remained so until 1971 when the American Medical Association published recommendations on the techniques of oral methadone maintenance [53]. In that year an estimated 25,000 persons were maintained on methadone [10]. In 1975, over 700 methadone programs maintained over 100,000 patients on methadone [55]. But the end of the historical cycle differed significantly from the start. The narcotic clinics gave their patients morphine tablets to take home for self-administration, with the risk of diversion to illicit use. Because one daily oral dose of methadone maintains a fairly smooth dependence, only in conditions of special need is the drug given to patients to take home for self-administration. Also in the 1970's, in contrast to the 1920's, the conditions and procedures of maintenance are closely regulated by Federal and State agencies. Methadone maintenance developed amid controversy, and enthusiastic advocates overestimated its success [46]. Like the advocates of the previous narcotic clinics, they asserted that addicts on methadone gave up criminal activities and obtained employment. Many persons dependent on a morphinelike drug have improved their social performance while on methadone, but methadone maintenance does not invariably change delinquent characters into stable citizens, it does not relieve chronic dysphoria, and it seems to attract and hold only a portion of the population of persons dependent on morphinelike drugs.

Detoxification has become the new name for drug withdrawal. It basically consists, as it did 50 years ago, of rapid or slow reduction to zero of the daily dosage, with the exception that methadone is usually substituted if the person is using heroin or another morphinelike drug. In the 1970's, as in the 1920's, new procedures and substances continue to be advocated for treatment of early abstinence. Among these are: self-regulated detoxification [60], electric convulsions [65], acupuncture [25], haloperidol [31], and propranolol [21]. Systematic followup studies of these treatments have not been published.

Drug-free treatment includes counseling, psychotherapy, therapeutic community, and other forms of treatment in which drugs are not used for treatment of the drug dependence. Transcendental meditation has been used [7], and behavioral treatment [14]. Systematic followup studies of these relatively new treatments have not been published.

Studies of the utility of narcotic antagonists continue. Among the several antagonists available, naltrexone appears to have several advantages [51].

With the transfer of the two institutions to the Bureau of Prisons, another historical cycle was completed. In the 1930's Federal prisoners addicted to narcotic drugs were moved out of the Bureau of Prisons into the two Public Health Service hospitals. Then in the 1970's, nearly 40 years later, all prisoners addicted to narcotic drugs were returned to the care of the Bureau of Prisons. But the end of this cycle differed significantly from the start. In 1935 the Bureau of Prisons had no special services for narcotic drug users; in 1968 the Bureau began to establish special rehabilitation programs for drug users, first for addicts committed under title II of the NARA, and later for other inmates considered to be drug abusers. Postinstitution supervision was provided for NARA addicts, and for prisoners who were released on parole. In 1971 the Bureau had drug abuse programs in 16 of its institutions [16]. All utilized some form of the therapeutic community model of treatment.

Assessment

The followup studies and anecdotal information show that some patients ceased use of morphinelike drugs for long periods after leaving the hospitals, but these patients represented a small minority. At least nine of ten patients resumed use of a morphinelike drug within 5 years after discharge. Few enduring cures of the drug-using habit were achieved. In widespread professional and public opinion, the hospitals came to be considered failures; measured by a criterion of enduring cure of most patients, they failed. However, in 1975, no other institution or treatment method has produced controlled outcome studies which demonstrate a higher rate of cures of drug dependence of the morphine type than that obtained by the hospitals.

Although they failed to find a cure for drug dependence of the morphine type, in historical perspective the two hospitals made important contributions to the treatment of the drug users.

They maintained a tradition of medical concern for the drug users during many years when physicians only rarely attempted to treat the drug users.

They provided a training ground for physicians and other professional workers. Public Health Service medical officers often reluctantly accepted assignment to the Lexington or Fort Worth hospitals, but once there they became intrigued by the clinical problems of their patients. Many of the physicians who obtained their first clinical experience with drug users at Lexington or Fort Worth subsequently worked at other locations in teaching, research, or community service in the field of drug dependence. A partial list of young physicians who left Lexington or Fort Worth to become leaders in drug dependence service or research includes: Paul H. Blachly, Everett H. Ellinwood, Jr., Joel Fort, Frederick

B. Glaser, Patrick H. Hughes, Jerome H. Jaffe, Herbert D. Kleber, Marie E. Nyswander, and George E. Vaillant.

They maintained a scientific tradition. In this respect the hospitals had a good start under Kolb's leadership, and with a research division which later became the Addiction Research Center. Hospital staff members produced a small but steady stream of clinical papers, some cited in the references to this chapter, in which they described the characteristics of patients, the treatment programs, and the problems. Treatment innovations which, in a few instances, included attempts at controlled evaluation were developed and described. These descriptive reports stand in marked contrast to other published reports consisting of unsupported advocacy of one or another special treatment.

In maintaining a scientific tradition, the hospitals debunked treatment assumptions. They found that all withdrawal treatments worked with about equal success, because the abstinence syndrome subsides regardless of treatment. They showed that comprehensive institutional rehabilitation affected few voluntary patients because the patients did not stay to participate in it. Furthermore, many prisoners and others under legal coercion, who seemed to participate in therapeutic activities during hospitalization, resumed drug use after discharge. These patients were undoubtedly affected by hospital treatment, but not sufficiently to cease drug use. And the hospitals demonstrated that aftercare did not markedly improve results, as measured by abstinence from morphinelike drugs. The debunking of treatment assumptions, including their own programs and innovations, probably contributed to the eventual closure of the two institutions.

The community mental health center movement, and its offshoot, community-based treatment of drug dependence, made large and geographically remote institutions obsolete, and perhaps the size and location of both the Lexington and Fort Worth Centers limited their potential for clinical research. But the need for a Federal clinical research facility for drug abuse has recently been emphasized. In 1975, after comprehensive study of the NIMH research program, an NIMH Research Task Force [63] recommended:

> An intramural facility should be established for treating and doing research on drug abuse and addiction. The need for such a facility is particularly urgent because the Clinical Research Center, Lexington, has been closed.

Physicians who served as medical officer in charge, in chronological order.

Lexington	*Fort Worth*
Lawrence Kolb	William F. Ossenfort
Walter L. Treadway	Grover A. Kempf
J.D. Reichard	William F. Ossenfort

Lexington—Con.

Victor H. Vogel
Kenneth W. Chapman
James V. Lowry
Murray A. Diamond
Robert W. Rasor
Harold T. Conrad

Fort Worth—Con.

Richard E. Holt
John A. Trautman
Robert W. Rasor
James F. Maddux
Warren P. Jurgensen
Dominick J. Lacovara

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Reflections on the Narcotic Farms

Robert W. Rasor, M.D.

Is there anything to say that is worth saying after 20 years in institutions for the treatment of drug addicts? The experience has been unique and it should be worthwhile to reflect on what, if anything, has been learned.

Psychiatry had been my interest even before medical school. After an internship and a few years in general medicine, followed by a brief training period in neuro-psychiatry, I was assigned to the USPHS Hospital in Fort Worth, Tex., as a psychiatric resident.

The original plan for the Fort Worth Hospital was to be an exclusive treatment center for narcotic addicts. In 1942, soon after its opening, it was designated a primary treatment center for psychiatric patients from the Navy, Marines, and Coast Guard. Admissions included drug addicts in small numbers, prisoners, male and female voluntary patients as well as some nonmilitary, nonaddict, psychiatric patients. This was the situation when I was assigned in 1947 to the Narcotic Hospital. It was a busy and interesting institution under a dual command—The Public Health Service and the U.S. Navy; Naval Medical personnel worked side by side with Public Health personnel; a fully accredited psychiatric residency training program was conducted.

After 1 year at Fort Worth, I was fortunate to be sent to the University of Chicago and the Chicago Institute for Psychoanalysis to complete my psychiatric and psychoanalytic training.

As a physician trained in psychiatry and psychoanalysis, my interest was "mental illness," drug addiction was a "mental illness" and drug addicts were "patients with mental illness." It was the task of the psychiatrist to treat the "addict" in such a way that he or she might be helped in overcoming his addiction. My knowledge of pharmacology was limited; the "age of pharmacology" had not yet arrived. Psychiatric treatment was not specific in relation to addiction.

With this background, I was assigned to the USPHS Hospital in Lexington, Ky. At that time, the hospital was operating at maximum capacity admitting about five thousand addict-patients a year. It was also a very active training center for all categories of mental health personnel. From 1951 to 1957, I was assistant chief of psychiatric service, chief of the service, and later, director of the residency training program.

In 1957, I was transferred back to the USPHS Hospital in Fort Worth as Deputy Medical Officer in Charge and later became Medical Officer in Charge. At that time, the patient population was made up of psychiatric patients from the Veterans Administration, some "Executive Order" patients who had been transferred from Saint Elizabeths Hospital in Washington, D.C., some male addict patients both prisoners and volunteers, and other USPHS beneficiaries with mental illness.

In 1962, I was reassigned to the Lexington Hospital as Medical Officer in Charge. Two months after assuming this position, a tragedy took place when a former nonaddict patient entered our home on the reservation and shot my wife, a patient working in our home, and myself. The wound that my wife sustained resulted in complete paralysis from the neck down and in her death 6 years later.

From 1962 until 1967, the hospital operated as it had in the past with male and female addict-patients, prisoner and voluntary, and some nonaddict patients.

Before considering the transition that was to begin in 1966 as a result of new legislation and a change in treatment philosophy, it is well to take a quick look at prior legislation and treatment philosophy.

Prior to the end of World War I, there was little concern with the problem of narcotic addiction in the United States. After the war, newspaper feature articles and editorial comments became common and the public looked upon the addict as a mentally deranged "dope fiend." There was no recognized scientific data on drug addiction.

In the early 1920's, the U.S. Public Health Service assigned Dr. Lawrence Kolb to conduct field studies on the nature and extent of narcotic addiction and to carry out experiments on animals. Dr. Kolb estimated that there were about 110,000 addicts in the United States, the majority of whom were nervous, unstable individuals. He pointed out that the drug-addiction problem was largely a psychiatric disorder [1, 2].

In January 1929, the 70th Congress approved an act: "To establish two U.S. Narcotic Farms for the confinement and treatment of persons addicted to the use of habit forming drugs who have been convicted of offenses against the United States. . . . Any person, except an unconvicted alien, addicted to the use of habit forming narcotic drugs, whether or not he shall have been convicted of an offense against the United States, may apply to the Secretary of the Treasury, or his authorized representative for admission."

"No such addict shall be admitted unless he voluntarily submits himself to treatment for the maximum amount of time estimated by the Surgeon General as necessary to effect a cure unless suitable accommodations are available after all eligible addicts convicted of offenses against the United States have been admitted. The Secretary of the Treasury may require any such addict voluntarily applying to pay the cost of his subsistence, care and treatment. Any person who submits himself for treatment shall not forfeit or abridge thereby any of his rights as a citizen, nor shall such submission be used against him in any proceeding in any court, and the record of his voluntary commitment shall be confidential."[3]

The treatment philosophy in the planning phase of the institution had its origin in the puritanical ideals of the therapeutic value of work, sunshine, and fresh air. The institutions were known as "Narcotic Farms" exemplifying the thinking of the founding fathers. There was no doubt that they were designed as prisons characterized by the imposing bars and grilles that greeted one at the entrance, the same bars and grilles we did so much to disguise and eventually remove. The setting was rural, 1,200 acres in the heart of the Bluegrass, a more beautiful area could hardly be found, with cattle, a dairy herd, and later, a small golf course. It was referred to by some as a "prisonlike hospital" and by others as a "hospitallike prison." They did not want it to be a prison although it was designed for individuals who violated Federal laws. It was the responsibility of the authorities to see that the inmates remained in custody.

The name "Narcotic Farm" was soon changed to USPHS Hospital, in part due to the confusion and kidding resulting from the logical question asked so many times, "Where do you grow the narcotics?"

From the beginning, there was the precarious and conflicting union of health and custody, treatment and security, medicine and penology. Early personnel came from the Public Health Service and the Bureau of Prisons. Blending the conflicting philosophies was not easy or always successful.

During my terms of duty, the treatment program was based on what I would refer to as "dynamic psychiatric principles." It was an eclectic-approach, individually oriented, using what I would consider fundamental psychiatric, psychoanalytic, psychological, and sociological principles. It was a program utilizing educational, vocational, spiritual, occupation, recreational, and psychiatric treatment. Group therapy was a major portion of the program with several hundred patients participating.

When the hospital opened, it was assumed that the staff had the authority to detain patients against their will. The act stated, "no such addict shall be admitted unless he voluntarily submits to treatment for the maximum amount of time estimated by the Surgeon General to effect a cure." However, in the first year of operation, a voluntary patient was released on a writ of habeas corpus and went before the judge in the Federal district in Lexington. The judge ruled that the patient had voluntarily committed himself and could voluntarily demand his release.

From the onset, the hospital operated two programs for addict patients. The primary one was for Federal prisoners addicted to drugs and the secondary program was for the so-called voluntary patient. Both programs had many limitations. The hospital had little control over the types of prisoners who would be admitted, how long they would stay and there were practically no provisions for aftercare. The majority of the voluntary patients left against medical advice after a very brief stay. The distance of the hospital from the communities in which the addicts lived made it difficult to have continuity of treatment after leaving the hospital.

The mission of the hospitals changed drastically with the passage of the Community Mental Health Center Act in 1968 [5] and the Narcotic Addict Rehabilitation Act 1966 [4] and the reorganization of the Public Health Service in 1967.

The intent of the Community Mental Health program was to center all mental health at the community level. With the reorganization of the Public Health Service in 1967, the National Institute of Mental Health became one of the five operating units of the PHS. The two Narcotics Hospitals were transferred from the old Bureau of Medical Services to the NIMH, and their names were changed to Clinical Research Centers. The new mission was spelled out as "one of clinical research in the field of drug dependence; to experiment with new techniques in the rehabilitation of individuals addicted to all types of drugs that produce physical dependency, and to carry out educational and demonstration projects that may be helpful to other agencies or governmental units with interest in the rehabilitation of drug dependent individuals."

At about this time, the Narcotic Addict Rehabilitation Act of 1966 became law. The act provided for both institutional and aftercare and civil commitment for treatment of persons charged with Federal offenses in lieu of prosecution, of committed offenders in lieu of sentence, and of nonoffenders. In the initial period, institutional care was to be provided at the Lexington and Fort Worth hospitals and gradually shifted to community agencies under a contractual agreement.

In 1967, steps were taken to stop the admission of voluntary patients. Agencies were informed of the provisions of the NARA legislation and they were encouraged to make the information available to their clients who sought help for their addiction. Soon thereafter, prisoner-patients were no longer admitted to the hospitals and were sent instead to correctional institutions of the Federal Bureau of Prisons.

The prisoner-patients had made up approximately two-thirds of the population numbering between five and seven hundred patients. All patients who were physically able were given a vocational assignment as part of the total treatment program. At that time, it was more acceptable to consider work as a form of therapy, making every effort to make the work as meaningful as possible. Vocational training and good work habits were emphasized. Assignments were made considering the needs of the individual and the needs of the institution.

Many patients were assigned to the working capital industries including the farm, woodcraft, needle trades, and printing. The industries were an essential part of the institutional treatment program from the onset. They were modeled after the working capital industries of the Bureau of Prisons. Prisoner-patients earned industrial good time and in this way the length of their sentence was reduced.

Patients were also assigned to the food service, nursing, sanitation, laundry, maintenance, and other areas of the hospital. The institution depended on the patients in vocational assignments for the every day operation of the hospital. With the phasing out of the large number of prisoner-patients, the daily problems of operating and maintaining services such as food, laundry, and sanitation became more difficult. The working capital industries were gradually phased out, starting with the agriculture industry, later needle trades and woodcraft with only printing remaining. As the patient population diminished, remaining patients were assigned to the most essential services and more full-time employees were added as funds became available.

Seminars and workshops were conducted with small groups of staff in an effort to bring about change in as orderly a manner as possible. Such meetings were held outside hospital environs in a relaxed atmosphere with all levels of staff participating. Consultants familiar with group discussions and problems in changes in attitude and roles were utilized. Such meetings went on over a period of many months and did much to reduce the anxieties and insecurities of staff members.

Efforts were undertaken to make the institution less prisonlike and more of a rehabilitation center. Many bars and grilles were removed and living areas were modernized with attractive furnishings.

The first NARA (Narcotic Addiction Rehabilitation Act) patient, soon to be known as residents, was admitted on July 21, 1967, which marked the end of one era and the beginning of another. Such residents were admitted under title I and title III of the NARA Act. Individuals committed under title II were cared for by the Bureau of Prisons and were drug addicts who had been convicted of a Federal offense and committed to the bureau for treatment.

Before a resident was admitted for treatment, he was required to undergo examination and evaluation for a period up to 30 days. He had to be seen by two physicians, one of whom was a psychiatrist who would answer to the court (a) whether the resident in question was an addict and (b) whether he was likely to be rehabilitated by treatment. If the addict was thought to have rehabilitation potential, he was admitted to the program. Early in the program, less than half of the addicts evaluated were accepted for treatment; the remainder were referred back to the community or the local court having jurisdiction.

The NARA residents were no different than the addict-patients who had been traditionally admitted to the hospital, either as voluntary or prisoner patients. Over one-third were under some type of pressure from State or local courts and came into the program to avoid prosecution. Initially, it was the understanding of the institution that such residents, once accepted in the program, could be held against their will. This proved to be unenforceable and unconstitutional. This meant that unmotivated individuals could not be held and many eloped or absconded from the center. Residents were informed that, if they escaped, the committing Federal court would be notified and any State or local court having jurisdiction would be advised. However, this did not serve as a deterrent.

The uncertainty regarding the authority of the center and the confusion in the legal interpretations contributed to the dissention and confusion among the staff and residents. The staff made every effort to bring about an orderly transition from a prison type hospital to an open and permissive clinical rehabilitation center. Security had been deemphasized and residents were given more responsibility for their conduct. The rapidity of the changes created an unstable situation which resulted in much anxiety and tension in the staff and residents. Changes in attitudes did not keep pace with physical changes. This was the general state of affairs from mid-1967 to mid-1969.

As Medical Officer in Charge, it was my responsibility, as I saw it, to create and maintain within a prisonlike psychiatric hospital a climate or atmosphere where prisoner and voluntary addict-patients had an opportunity for rehabilitation. Efforts were made to make it a stimulating atmosphere for staff; training and staff development were carried out and research was encouraged. As is always the case there were limitations and deficiencies. Staff turnover, particularly physicians, presented difficulties in continuity of treatment. The physical facilities imposed limitations in living assignments and separation of patients, volunteers and prisoners, men and women, and always there were nonaddict patients to be cared for. The responsibility for custody for some 700 prisoner-patients was always present. The maintenance of a drug-free environment was essential to the treatment program and required constant attention to the introduction of contraband drugs.

Dr. Lawrence Kolb, the father of the PHS addiction treatment program, introduced the concept of narcotic addiction as a health problem some 50 years ago. Throughout his long and productive career he championed the concept of addiction as a medical problem and deplored the harsh sentences imposed on drug addicts. In spite of his efforts and those of others to decriminalize drug addiction, legislative trends for stiffer sentences continue, the New York legislation is the best example.

I would not go as far as some who would propose the elimination of all laws pertaining to what drugs a person may take. However, I would recognize the difficulties in legislating what a person may or may not take into his body. As one who lived through the prohibition era with all the related problems I feel that we must recognize the limitation of law in this field. There should be laws for the control of dangerous drugs and addicting drugs, including alcohol. These are dangerous drugs, they are toxic and lethal when taken in sufficient quantities. Laws should relate to the manufacture and sale, with proper labeling and warning of inherent dangers. Crimes committed by individuals should relate to the criminal act, such as robbery, murder, illegal manufacture, illegal sale.

Drug addiction is not only a medical problem, but a social problem as well; I would prefer to refer to it as a medical-social problem. It involves an individual in a social environment where addicting drugs are available. Any individual under the proper set of circumstances may become addicted, but some individuals are more susceptible than others. There is a breaking point for all humans; beyond this point, pain, suffering, frustration, and disappointments become unbearable; deviant behavior results such as psychosis, suicide, drug dependency, etc. Some individuals are not well suited to meet all the anxieties, tensions, disappointments, physical and psychological pain and suffering that they are exposed to in this imperfect world in which we live. The stresses and strains of our modern society become more complex and more disconcerting all the time and this is no doubt related to the increase in the use of addicting drugs. Many of these drugs, alcohol, opiates, cocaine, marihuana, have been with us for a long time and mankind has been using them to relieve pain and discomfort and will no doubt continue to do so. To expect a pure medical solution to this problem is expecting too much.

A broad approach is necessary with emphasis on (a) education, recognizing the limitations and hazards of education; (b) rehabilitation, using various models that can and are being evaluated; (c) sensible laws for the control of dangerous drugs; (d) research; physiological, psychological, pharmacological, sociological, and rehabilitative.

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DR. ROBERT L. DUPONT, *Director,*
National Institute on Drug Abuse

The Addiction Research Center— The Second 40 Years

Robert L. DuPont, M.D.

Helping to commemorate the founding of the hospital here and the beginnings of the Addiction Research Center is for me a complex emotional experience. It's reassuring to recognize that our present drug-abuse research effort is a linear descendant of this distinguished program which has now spanned 4 decades. It's also humbling to realize that here, before the days of big budgets, a brilliant handful of scientists wrote an impressive chapter in drug-abuse research history.

The names of those involved are a *Who's Who* of distinction in drug research: Nathan Eddy, Lawrence Kolb, C.K. Himmelsbach, Bob Felix, Harris Isbell, H.F. Fraser, Abe Wikler, Harris Hill—to name but a few of those earlier researchers.

Dr. Robert C. Petersen, *Assistant Director, Division of Research, National Institute on Drug Abuse, who represented Dr. Robert L. DuPont at the Symposium*

The accomplishments of ARC have been distinguished. Others are better equipped to discuss them in detail, but let me remind you of a few among many which have profoundly affected the course of our drug-abuse thinking:

1. Elucidation of the basic metabolism of morphine and heroin.
2. Demonstration of the abuse potential of methadone and a recognition of its potential value in detoxification treatment.
3. Recognition and explication of the important role that conditioning and secondary reinforcement play in opiate-abuse relapse.
4. Pioneering studies of marihuana. These included determining that delta-9-THC is the major psychoactive component and a hallucinogen in its own right.
5. Demonstration of the alcohol and barbiturate abstinence syndromes.
6. Initial studies of narcotic antagonists and early recognition of their possible therapeutic value.

From the standpoint of cost effectiveness, ARC has repaid its cost of operation many times over through its drug screening efforts alone. Let us assume that the introduction of an uncontrolled new drug with high abuse potential were to occur. As a result, we might well expect at least a

1 percent increase in the number of those seriously abusing drugs. A minimal estimate of those addicted runs about 400,000. This means that such a new drug would increase this population by about 4,000. The cost per year per addict to society has been conservatively estimated at $10,000—and that's just the amount of lost income and cost of treatment services. It does not include the cost of human misery to addicts, their families, and the larger society. Multiplying this $10,000 figure by the hypothesized 4,000-person increase equals $40 million. That's nearly 20 times the present annual budget for the Center. Dr. Martin assures me the Center's drug-screening efforts prevent the inadequately controlled distribution of at least two drugs each year.

The distinguished record of this Center demonstrates, far better than any rhetoric ever could, the importance and essential need for a strong intramural research effort if we are to promote a tradition of scientific excellence. Let me here assert unequivocally my personal commitment to the enhancement of NIDA's intramural research effort.

Having been much involved with the growing public awareness and rapid growth of drug abuse prevention and treatment activity, I am aware of the need for service programs to be built on a foundation of basic research knowledge.

There are many temptations to try to shortcut the process of developing that basic knowledge. One obvious hazard of the public concern about drug abuse and its translation into research appropriations has been the insistence that answers be rapidly forthcoming. Yet, it is only now after many years of research that we are gaining the basic knowledge of the mechanisms of the opiate receptor that may prove most crucial to better opiate-abuse prevention and intervention. Thus there is a decided need for a steady, solid research effort independent of a sometimes fickle public concern about the drug-abuse problem.

It is only through a long-term commitment to a continuing research effort that we can guarantee that research will continue in the orderly, productive way it has here at ARC throughout the years.

Moreover, the Center has been the source of significant leadership extending far beyond Lexington. It has served as a major training ground for many able researchers who have gone on to continue to pursue elsewhere their careers in drug-abuse research. Modestly sized intramural research programs are often more ideally suited to meet this need than are grant-supported projects in the larger scientific community.

It is also worth noting that the present National Institute of Mental Health, and indeed the entire Alcohol, Drug Abuse, and Mental Health Administration, are direct descendants of what was begun here at Lexington. Robert Felix and Stanley Yolles, together with others too numerous to mention who received training here, have gone on to leadership positions in drug abuse and mental health more generally.

Because of its close affiliation with the U.S. Public Health Service Hospital here, ARC staff have been involved in the realities of patient-treatment. This has frequently led to a more sensitive pursuit of basic research directions than is found in more typical basic research settings far removed from clinical reality. Had it not been for awareness of the high rate of recidivism, ARC might not have given as much thought to the role played by conditioning and long-term physiological changes in predisposing the addict to relapse.

Although there are very real advantages to engaging the interest of the larger scientific community in drug abuse related research, it is also worth remembering the impressive output of high quality scientific work that can result from such a small cadre of dedicated and talented researchers such as ARC represents.

Given the obvious history of accomplishment here, it may seem gratuitous for me to urge us all to still greater effort. Perhaps it is in the nature of administrators to "dream the impossible dream," or my impatience for research progress may be because of my having had to contend with the realities of prevention and treatment. In any event, there are several things that concern me about our present NIDA program. Many who provide prevention or treatment services appear to be content to go on doing so uncritically. There is too little concern to be self-critical or to raise the thorny questions of what works best with whom under what circumstances. Many millions have been invested in response to the public demand for drug-abuse services despite limited evidence for their efficacy. Indeed, there is the distinct possibility that under some circumstances our efforts may, in fact, encourage increased drug use. I'm thinking specifically of large-scale drug-abuse education efforts in communities where there is little evidence a problem exists. Under such conditions it is quite possible that adolescent curiosity may be aroused by the educational program itself. This may well lead to more experimentation than might have occurred based on their initial interest alone.

Before we become too self-congratulatory while wearing our researchers' hats, we might also remember that we too have a tendency to do what comes most easily or comfortably. It is often easier to limit oneself to basic research or to well-controlled laboratory settings than to attempt to cope with the messy problems of the real world.

It has been my despair and that of my predecessor, Dr. Jaffe, a distinguished researcher in his own right and an illustrious ARC alumnus, that so little research has been done to guide us to wiser program decisions. We need well-designed and well-executed research to choose between program alternatives and to ensure that our limited resources are wisely applied. Too often the most gifted researchers have scorned practical problems as either inappropriate or poorly suited to the well-controlled research conditions their career contingencies lead them to prefer.

Nevertheless, it is people who abuse drugs, and not rats. And drug abuse must be prevented not in laboratory animals but in people living in a complex world. Let me try to be specific about some of our problems:

Drug abuse, if we include the use of alcohol and tobacco, is a significant factor in morbidity and mortality from such diverse sources as pulmonary disorders, heart disease, hypertension, and motor vehicle industrial accidents. If we could prevent or significantly reduce substance abuse, we would make greater inroads into these problems than through any other public health measure. Yet the number of those actively working on better understanding the psychosocial, cultural, and biological approaches to prevention is quite modest. Our understanding of the contributing factors to serious drug abuse even in high-risk groups is very limited.

Despite the millions that are being invested in treatment services, our understanding of what works best with whom under what circumstances remains rudimentary. Those providing drug-abuse services continue to be preoccupied with the mechanics of their profession rather than asking about how to improve treatment efficacy. We can do better.

There is a compelling need for researchers to shape research questions in ways that are relevant to the problems of coping with drug abuse in the real world. In this I am *not* trying to encourage a short-sighted emphasis on immediate results or even on applied research. I am well aware that such an approach may not only fail to solve our problems but may also divert precious resources from areas that would ultimately have proved to be most productive. Had we, for example, devoted all our polio-research dollars to ameliorative treatment research, we might have delayed the breakthrough that came through virology. Because of a modest investment in the development of vaccines, polio is now largely a disease of the past. But, by the same token, had Enders, Salk, Sabin, and others given no thought to polio and its prevention as a practically important research problem we might still be contending with periodic polio epidemics.

Even as a balance must be struck between basic and applied research, we must give concern to the relevance of our research efforts to the human problems which justify their research support. Too often and in too many areas research has presented a sizeable investment based on a promissory note on which the interest has yet to be paid.

Many examples have been and will be cited of past research leadership here at ARC. The opportunities for future leadership are equally real. The problem of drug abuse is not likely to diminish in importance although the degree of public alarm and interest may well do so. But regardless of the priorities drug-abuse research receives from the public, we have the chance to provide a model of effective research directed toward alleviating a social problem. If we are able to be in the vanguard in devising relevant research, there is little doubt that the extramural research effort will also increasingly reflect this.

ARC's location here in Lexington is both an asset and a liability. Its distance from major metropolitan centers can provide a measure of detachment sometimes helpful, but it also demands special effort if ARC is to be in close contact with the changing drug picture. As the data on the Vietnam veteran illustrate, heroin addiction may be more than the simple extension of preexisting psychopathology. We need to know more about the role of situational determinants in influencing drug-abuser careers. The study of returning Vietnam veterans also showed that, at least under some circumstances, the traditional pattern of repeated relapse does *not* occur.

One of the emerging realities is that heroin addiction previously largely confined to a few coastal cities is now a national problem to which no city is immune. The Addiction Research Center could well be in the vanguard in studying contemporary addiction in these rural and smaller urban centers. By studying emerging addiction in such locations we may learn much about newer drug-abuse patterns, their dynamics, and more effective responses to them.

It is my strong belief that we can achieve a greater degree of practical relevance without compromising our research excellence. In fact, in those situations in which the clinician has sat down with the "bench scientist," both have frequently profited. The clinician on his part is likely to be reminded of the need for careful, objective, and systematic evaluation of his therapeutic efforts if they are to be truly rational. The researcher is far more likely to generate hypotheses and to devise research paradigms that reflect the actual circumstances of drug abuse in our society. He is likely to give greater attention to the possible utilization of his research findings in shaping new approaches to prevention and treatment and to do so on a continuing basis.

Inevitably, at least some of the time, we will find that our research models are inadequate to describe the real life situation. This should not be a signal to retreat to the safety of the academic community where we receive reassurance from our fellow researchers that all is not well in the real world. If we can translate our insecurity into efforts better approximating the real world of drug use and abuse, we are likely to make the second 40 years still more distinguished than the first. In the process we can also provide an impressive demonstration of the relevancy of the scientific method to the solution of a major social problem.

Today's treatment and research situation is vastly different from that of 40 years ago. A small band of dedicated people has grown to include many thousands working throughout the United States. While research was once a very small enterprise, it is now a very large one. This widespread treatment and research support picture contrasts sharply with previous decades of relative neglect. But if the present is far more complex than the past, the challenge to provide increasingly more effective leadership is even greater. It is my hope that the Addiction Research Center will help to provide that leadership.

Dr. William Pollin, *Director, Division of Research, National Institute on Drug Abuse*

Drug Abuse and Biomedical Research: Circa 1975

William Pollin, M.D.

As the initial title of my paper (The Federal Drug Abuse Research Program: Current Dimensions, Priorities, and Trends) indicated, my original intent, when Bill Martin invited me to participate in this felicitous 40th anniversary meeting, was to attempt to place the history of the Addiction Research Center into current context. I planned to summarize the current total Federal program and drug-abuse research so as to clarify and emphasize the uniquely valuable and crucial role of the Addiction Research Center past and present, and its future potential.

This was a feasible goal—such an overall description—due largely to the initiative begun by Dr. Jerome Jaffe and his staff at the Special Action Office for Drug Abuse Prevention some years ago. Working with Dr. Jack Mendelson, they planned a systematic and comprehensive identification and categorization of every federally funded research project in the drug-abuse area. This initiative, continued under Dr. Robert DuPont, has given us a more complete view of the total Federal research effort in drug abuse than is available in most other Federal biomedical research areas.

However, as I have listened these past 2 days, I found a different but related issue increasingly occupying my thoughts. As our famed predecessors and productive current colleagues shared their uniquely personal recollection of an important scientific and institutional history with us, I frequently found myself recollecting where I was and what I was doing in the years they described and what the events and moods of the country were during those years.

As I did so, I was struck increasingly by the extent of the external changes, the national changes which surround the local history we have found so stimulating. At one level there has been the ebb and flow of national concern and awareness concerning drug and substance abuse. But the elements of the changing environments that influence our scientific endeavors encompass a much wider span. During these 4 decades of growth, and particularly during the last one, intellectual, political, social, and scientific changes of major proportions have occurred. These are changes which it seems to me we must perceive clearly, and deal with effectively, if the 40-year growth and accomplishments of the Addiction Research Center and the Larger Federal biomedical research establishment it helped to spawn are to serve as a foundation upon which to build rather than a peak from which we descend.

I've decided, therefore, to modify my presentation considerably. I will spend little time describing the content of the current total Federal program. Toward this goal primarily I will call your attention to the summary analysis and directory of all projects and researchers now available from my office and invite those interested in obtaining copies to contact me in Rockville. This summary contains descriptions in considerable detail of the programs of ten Federal agencies involved in drug abuse research, changes during the years 1972–74 in priorities, and lists by name and title all investigators and researchers who have been funded during these years.

I will concentrate instead on attempting to summarize my personal view of the changes in the larger system we are part of—which includes not only the total Federal drug-abuse research effort but the overall Federal biomedical research system and the national scientific and health care systems. On the basis of this picture, I will suggest a change in our pattern of reacting to demands from this larger system, which it seems to me is essential if the progress of recent decades is to continue and move forward in the years ahead.

During the first 25 years following World War II, national investment in biomedical research climbed precipitously from tens of millions to over three billion dollars a year. Public and Congressional support for this enterprise seemed almost unlimited. In part, this resulted from the public perception of the apparently unlimited potential of science. Congress and the public were extrapolating the implications of the apparent conquest of infectious disease by antibiotics, development of nuclear power, and the atomic and H bombs. Simultaneously, Federal funding of biomedical research fell under the aegis of a fortuitous grouping of unusual men, who combined a sincere concern for the public welfare and a commitment to the science of health with shrewd political skills—including notably Felix, Shannon, Hill and Fogarty. As a result, during many of these years, the struggle of NIH was to spend effectively the moneys often urged upon it by the public's representatives above and beyond its own requests.

It was during this period that the health-care system began to be seen as a science-based industry. Whereas prior to 1950 less than 1 percent of the gross revenues of the health industry (using total expenditures as equivalent to revenues) was spent on research and development, by 1966 this had increased to 4.8 percent. Though this seems to be a substantial investment, two points require emphasis: first, most successful science- and technology-based industries have spent from 8 to 15 percent of their revenues on research and development; second, in recent years the Federal percentage has fallen from 4.8 percent to less than 3.5 percent. Thus, in the current year, over $104 billion will be spent on health care, not counting social costs or suffering, and only about $3.5 billion on all biomedical research and development.

In the drug-abuse area, the period of rapid increase has been much more recent, but interestingly, we seem to have peaked out at essentially the same point. During the past 10 years, NIDA (and its NIMH predecessors) has increased more than tenfold the moneys directed toward research. The last complete review (FY '74) identified some $55 million for the total Federal research effort and we assume $60 million will represent the national research and development figure in this area during the coming year. This projection assumes no new SAO funds, approximately $10 million in demonstration and services research, and 5 million research dollars in other agencies, such as the VA. So the drug-abuse research effort represents only 4.6 percent of the total national cost of drug-abuse treatment systems (again using program and health resources costs only), or approximately $.25/capita/yr nationwide.

We are all aware of widespread and growing doubt about the adequacy of return from the national biomedical research effort. To the extent that there is justification for such questioning, is the failure the result of excessive expectations, poor management, or inadequate research ideas? Or conversely, does it in part result from the fact that we have not yet reached that 8–15 percent of total revenue invested in research and development, which empirically, in other science-based industries, appears to represent the threshold of necessary critical mass?

Thus far, I am aware of no evidence or study which supports this latter conclusion, or evaluates the general issue. We should emphasize that of all categories of human behavior, one of the least researched is our own research behavior. Given the increasing pressure of other national priorities, it is widely assumed that, at best, we will be able to retain a plateau of Federal spending for these purposes in the immediate future. Some fear, indeed, that the time may come when absolute dollar amounts will be reduced.

Before considering this increased skepticism in greater detail, let me comment on some of the encouraging strengths of the present environment. These include acceptance of the continued essential role the Federal Government should play in supporting biomedical research; a growing awareness of the need to maintain stability in such research undertakings; and the quality of the men who have recently come on the leadership scene, or are in the process of doing so: Cooper, Frederickson, Isbister, and DuPont—knowledgeable, skeptical, aware of competing demands, but possessing a sophisticated grasp and respect for research.

The need for central Federal support of many health activities has been seriously considered and questioned, but this has not been true of research. Research, like national defense and police activities, is seen as yielding social benefit, rather than a product which can be divided into measurable units and directly benefit specific individuals. Additionally, there is growing awareness of the facts that approximately 70 percent of major scientific discoveries eventually put to practical use have been derived from research not classified as oriented to that final product or mission when first conceived; and also that the time scale by which the benefits of basic research are measured tends to be decades, rather than months or years.

With regard to the need for stability of biomedical research, there is also growing awareness of the fact that high quality research activity cannot be rapidly expanded, in contrast to the rapidity with which funds can be cut and downward adjustments be made. Challoner [2] has pointed out that biomedical research, being a highly labor intensive activity, utilizing personnel who require prolonged training and great skill, depends upon 7 to 15 years of training and working together to develop a productive team of investigators, assistants, and trainees.

Nonetheless, we must seriously ask ourselves: Is there substantial merit to the growing feeling that we have progressed more slowly than was anticipated 25 years ago, in developing knowledge able to impact significantly upon and basically alter the Nation's health needs? Such impact is the fundamental rationalization and justification of Federal programs in this area. But is it happenstance that the one disease which, in the public mind, is the model of a scientific triumph, namely, the events dealing with the "conquest of polio," was the one disease where a substantial part of the research effort was *not* funded or directed by the Federal Government? Unfortunately, this question arises at a time of growing national skepticism and doubt concerning science, a skepticism which often goes beyond useful challenge, in my view, and instead reflects part of a dangerous nihilistic anti-intellectualism. The increased public interest in nonsciences such as astrology and demonology, the popularity of the Dr. Strangelove and the Clockwork Orange stereotypes depicting science appropriated for berserk or antihuman ends, are part of this trend. On a more substantive level, the exaggerated view of the capacity of science to solve all problems quickly, prevalent in the early post-World War II days, seems now to have swung too far in the opposite direction. Now science's dangers rather than its potential are emphasized. Hopefully, the time when the thesis and antithesis will be reconciled by the productive Hegelian synthesis is not too far in the future.

In the interim, however, this generalized tendency to question science in general has been reinforced in a particularly dramatic form in the fields of medicine and biomedical research. If we merely list the major new influences of recent years which have or are likely to impede significantly the mere mechanics of conducting biomedical research, the combined impact can be staggering. Many of these new considerations, individually, emerge from or are themselves desirable, necessary steps forward. But coming along in a helter-skelter, uncoordinated fashion, they create what at times feel like almost insuperable obstacles to planning and conducting research. There is the Freedom of Information Act, for example, with its requirements which not only threaten an investigator's right to his own creative hypotheses, but at points seem to run directly counter to other mandates concerning confidentiality principles and patients' rights. Complex ethical and legal problems of informed consent are made more complex, and in some instances insoluble, by contradictory court rulings mandating patients' rights for treatment in some instances, and rights to reject treatment in other instances. Third party payments, the coming of National Health Insurance, and resultant demands for demonstration of treatment effectiveness, have brought a sharp increase in concern about the proper Public Health Service research role, and extent of activity, in conducting definitive clinical trials. Unfortunately, our methodology here is often limited and primitive. Frequently the only model which can be visualized is the large-scale multiyear prospective study, exemplified by the recently completed Heart Institute study of Atromid-S. This gave a definitive answer to a limited question, but required $40 million over a 5-year period.

I have expanded on these general problems as a background for raising the question of priorities in a somewhat different form than is usually the case. The question that arises is: Need we individually and/or collectively change our customary pattern of responding to issues of the type I have described? To be sure, similar ones, of lesser number and intensity, have always been with us. In the past, many of us, I believe, have relied on the Bob Felixes and Karst Bestemans and Bob DuPonts to carry the ball in these areas; and we have committed relatively little of our own creative resources to dealing with the substance of these questions. When pressed, our posture as researchers has been defensive and often self-righteous and annoyed. Survival, and continued growth, however, require new responses to new situations. I believe our situation has changed, and that the new response called for requires that we all widen our field of view, take some time from our own field of scientific study, and put these freed-up personal resources into dealing with the types of questions I have called attention to. We have no choice with regard to the possibility that these questions and challenges will go away—they won't, they will increase. The choice we do have is whether we will raise them—we, the scientific community, raise them—help formulate them realistically, and try to come up with meaningful answers, or whether we will stand by passively and defensively while nonscientist critics raise them and make political capital out of scoffing at research titles and projects whose scientific importance is obscure to the layman.

Only such widespread involvement can assure our ability to sustain the view of science and research shared and lived by many here. This view of science, articulated eloquently in Daniel Bell's book [1], I would like to repeat here.

> The community of science is a unique institution in human civilization. It has no ideology, in that it has no postulated set of formal beliefs, but it has an ethos which implicitly prescribes rules of conduct. It is not a political movement that one joins by subscription, for membership is by election, yet one must make a commitment in order to belong. It is not a church where the element of faith rests on belief and is rooted in mystery, yet faith, passion and mystery are present, but they are directed by the search for certified knowledge whose function it is to test and discard old beliefs. Like almost every human institution, it has its hierarchies and prestige ranking, but this ordering is based uniquely on achievement and confirmation by peers rather than on inheritance, age grading, brute force, or contrived manipulation. In totality, it is a social contract but in a way never foretold by Hobbes or Rousseau, for

> while there is a voluntary submission to a community and a moral unity results, the sovereignty is not coercive and the conscience remains individual and protestant. As an image, it comes closest to the ideal of the Greek polis, a republic of free men and women united by a common quest of truth. . . . The dedication to science has a hallowed quality, and because this partakes of the "sacred" we can say that the ethos of science describes a "charismatic community."

To sustain this view of science, and maintain its health and growth is one of our major goals. Achievement of this goal depends upon maintaining scientific excellence and productivity. Equally important, however, are two additional responsibilites: the need to pay our way by dealing effectively with health needs which are the public rationale for our being; and to be sensitive and involved with the broader cultural and social currents of our time.

In the area of drug-abuse research, the Addiction Research Center has been par excellence the national resource and national example that comes closest to fitting this eloquent description of Bell's. We look forward to its continued health and productivity as it sets the pace during the decades ahead, as it has during its first 40 years.

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Karst J. Besteman, *Deputy Director, National Institute on Drug Abuse*

The NARA Program

Karst J. Besteman

I'd like to talk about the Narcotic Addict Rehabilitation Act (NARA) and program this afternoon, a program about which I have a very paternalistic feeling. Sherman Kieffer asked me to join NIMH to implement the act. I didn't know what I was getting into at the time, so I said yes. My first introduction to the program was to attend a planning session in the Barlow Building which was also attended by Dr. Maddux, Dr. Rasor, and Dr. O'Donnell. Art Berliner, who was the chief social worker at Fort Worth, had been asked to write a position paper which was to serve as a focal point for discussion. He made the mistake of calling addiction a social problem with medical psychiatric characteristics. Maddux was at one end of the table, Rasor at the other, and I was in the middle. They insisted that drug addiction was a medical psychiatric problem with some social implications. Eventually we ignored the problem and began implementing the law. It is my fondest hope that it is now in its last years.

I'd like to start by telling you of some of the Congressional testimony which supported the legislation and which represented the collective wisdom of the Federal Government. Attorney General Katzenbach, in his testimony before the Senate Judiciary Committee, said the NARA recognized in law what had long been established in medicine, namely that narcotic addicts, even those who commit criminal offenses, should not be treated invariably as common criminals. Later he said, "I would not be here speaking in support of this bill if I did not consider it an essential part of our fight against crime. It is already unmistakably clear that until we find more adequate ways to handle narcotic addicts, we will be preserving a very large and avoidable part of our most dangerous criminal activity." Yet a little later in his testimony he said, "The real question is how much longer we can allow the public safety to be endangered by continuing the primitive, strictly punitive approach to addiction which has spread like a plague through some areas even as penalties against it have been stiffened. How much longer will we allow our crime rate to be fueled by laws that lag years behind medical research?" Possibly a relevant question for today.

Surgeon General William Stewart, whose testimony I'll summarize, stated that addicts should be in an institution for a year as part of their treatment. I don't know where he got the year, for it wasn't the policy at either hospital at the time. He also indicated that one of the reasons for the year was that if Congress passed a law, it would give the USPHS a year to implement the aftercare section. He said we were presently implementing the Comprehensive Community Mental Health Center Act under which authority we had awarded approximately 20 grants for developing centers for treating addicts. He summarized his position by saying, "I think on professional grounds we are very interested in making sure that the development of the care of the mentally ill and emotionally disturbed people is approached on as comprehensive a basis as we can. We are not compartmentalizing the treatment into categories of illness, such as addiction, narcotic addiction, or alcoholism or other mental illnesses." So much for the collective wisdom of 1966.

Dr. Rasor had expressed the view that, in general, in most communities there are not too many people who are particularly interested in or knowledgeable about drug addiction. In our larger cities there are some people who are knowledgeable and are competent to deal with drug problems. Manpower is one of the major problems. Trying to get people interested in working with the addict wherever you have addiction problems is difficult. His remarks were prophetic because in implementing the program, as I will point out later, we found an abysmal lack of knowledge in most communities. Essentially the NARA said that if an addict got in trouble with the Federal court, treatment would be provided as an alternative to sentencing. Under title I addicts could be committed to treatment before sentencing and under title II could be committed after being found guilty. There was also a proposed title III which allowed people to be paroled out of the Youth Corrections Act into civil commitments. Title IV made some vague comments about supporting States and communities in terms of community projects. When the law passed, there was a new title III which allowed any narcotic addict or relative of a narcotic addict to come to a Federal court and petition for commitment as a volunteer into a program that was not to exceed a 30-day examination and evaluation period, a 6-month inpatient period, and not to exceed a 3-year supervised aftercare. There is no legislative history on title III. There was no anticipation that title III would pass when the testimony was given. In testifying on the bill it was clearly understood that Lexington and Fort Worth would be used to help implement the Act. The number of patients that would be committed under title III was not known but was estimated to be about 900 admissions per year. The admissions, I think, at the peak year were something over 5,000.

In the reorganization, which was referred to earlier in Dr. Rasor's comments, NIMH inherited the two centers (I think it was January 1, 1967) and was directed to implement NARA on July 1, 1967. The total staff on July 1 consisted of three personnel in Sherman Kieffer's office of Director of Field Investigations. I arrived on August 1 and one more person arrived on October 1. We then hired 11 professionals with no experience. We didn't know about the tradition of the corps in giving young professionals a lot of responsibility to which Dr. Cameron earlier referred. We turned 11 neophyte professionals loose in New York, Chicago, and Los Angeles, with a long distance phone for supervision, to implement this act. Believe it or not, they pulled it off, with a little help from headquarters.

The Director of NIMH made a statement regarding the program in February 1967. Stan Yolles said that approximately 80 percent of the narcotic addicts were concentrated in 11 cities in the United States and therefore NIMH would open 11 clinics to implement the act. NIMH never opened a clinic to implement NARA. It was also stated that the PHS outpatient clinics would be used to help implement this act, and again, this never occurred.

From July 1967 to March 1968, we were in a quandary. There was no institutional precedence in NIMH for managing a direct program. NIMH had an extramural granting mechanism for the community mental health centers and for extramural research. What we were doing didn't approximate the nice on-campus intramural research that NIMH was familiar with. Further, we could find no one in the institute to give us guidance on how to write program specifications. How do you draft what we called the vending machine contract? We wanted to have a standard contract for all of our treatment facilities. The contract office said you negotiate each contract individually, which we thought was inappropriate since we wanted all of our contractors to render similar, if not identical, services. We visited the California Rehabilitation Center in Corona where I first met Dr. Vogel to learn how California implemented its civil-commitment program. We went to New York and to Synanon. In fact, some of our employees in the Los Angeles field office joined Synanon.

The system called for us to funnel patients from 96 Federal courts to Lexington or Fort Worth, and then to have contract programs in the community of origin. We found that River Bend, Oreg., and Ackerman, Miss., were centers of addiction. We were collecting what I'll call atypical addicts as the communities were referring their ne'er-do-wells to the NARA program. On the other hand, we were getting practically no commitments from New York, where a judge said the law was an unconstitutional law. He never ruled that, he just said it. In the Miami area another judge felt the law was unconstitutional. We spent a lot of time explaining the intent of Congress to Federal judges. The issue of the constitutionality of NARA has never been settled.

In 1968, 611 patients were committed. About half to two-thirds of those patients were rejected by the examining physician as either not being narcotic addicts or not being likely to be rehabilitated. Answers to these two questions were the legal basis for admission. Obviously no psychiatrist can answer these questions with any certainty.

The number of admissions in FY '69 was almost 3,500; our peak number of admissions was 5,500 in 1970, and it has declined since then. Only about 50 percent who were committed remained in the program, thus on the last day of 1971 we had 2,100 patients in the program; in FY '73, 1,500. We then initiated a policy to transfer NARA patients into community programs. As of the end of May 1975 we have 295 patients still in the NARA program, and it's our hope that by the end of this month it will be about 250. For the last 2 years the Congress has considered repealing NARA, but it still is in committee. One of my ambitions as a Federal bureaucrat is to see the repeal of NARA, but thus far I have been unsuccessful.

NARA was seen by the Justice Department, who proposed the bill, as a reform of the penal criminal justice system and to be more humane to addicts. NIMH had the responsibility for title III patients and established a program. The first 30 potential contractors met in March 1968 at the Barlow Building. They were given a 2½-hour briefing session on the legal aspects by a representative from the Attorney General's office on treatment principles and on their legal obligations. These were 100 percent contracts—the Government paid for everything. When we got through with the briefing; it was opened up to questions. The second question came from a psychiatrist who headed a community health center in St. Louis, Mo., a delightful woman who had done research on goldfish in trying to learn about schizophrenia. She asked, "Once we have an addict on an outpatient basis, what kind of maintenance electroshock therapy will he need?" Immediately an ex-addict who was running a therapeutic community in Connecticut erupted out of his chair and said, "Who is that crazy lady?" He would not even admit there is a possibility that there was any psychiatric component to drug addiction. He came out of the Synanon and Daytop traditions, and was a trifle upset by the thought of outpatient maintenance electroshock therapy. The psychiatrist from St. Louis got a contract, did provide treatment, and all went well. No patient received electroshock therapy at the community mental health center with which she was associated.

Detroit was a very large, troublesome center and referred more NARA patients to Lexington during a 2-year period than any other city. We found 89 percent were unsuitable for treatment. One Detroit judge believed that addiction caused most crimes. On one occasion he sent a man under charge of first-degree murder and who had previously murdered several other people to Lexington. This is what we were dealing with. We went to Detroit and talked with 55 potential contractors, the U.S. Attorney, and the Comprehensive Health Planning Board for a local treatment program. At the end of the meeting we asked how many would like to give services to addicts in Detroit and were willing to negotiate a contract on the spot. All 55 agencies got up and fled out the door. They wanted no part of it. The city-county health department as a public service entered into a contract with us against their better judgment. The program wasn't very successful.

At one point we had developed a network of over 150 contracts in 134 cities in the country—and this was before there was a large viable grant program. There were only between 6 and 10 narcotic treatment grants active at that time. NARA did develop a group of people around the country who at least could say, "I have treated an addict." When the need to mobilize other community treatment programs came about, there was an existing cadre who took over.

Further, Government had developed the management capacity to take care of contracts and grants that later became the backbone of a larger program. The Narcotic Addict Rehabilitation Grants which don't exist any more were first established in the Division of Field Investigations, and then Division of Narcotic Addiction and Drug Abuse. The employees became the major processors of community grants, distributors of money, and monitors of what was happening in the programs. Had NARA not started a few years before the big push and built some competence, I don't think we would have been able to carry out the management responsibility we were given in the early 1970's.

Because the institutional prejudices of NIMH were against methadone maintenance, drug-free outpatient treatment was stressed. We made it a rule that no patient that was civilly committed by a Federal court could be put on methadone maintenance without a specific case summary being sent to and approved by headquarters, with the intent of slowing down methadone maintenance. Further, several judges ordered that methadone maintenance not be used for civilly committed patients. These biases and court orders, however, forced us into examining what could be done on a drug-free basis.

There were several reasons why NARA contributed substantively to the closing of the Fort Worth and Lexington hospitals and the CRC's. As Dr. Rasor pointed out earlier, the admission of volunteer-patients and prisoner-patients was terminated. We thus had a closed system. Federal courts civilly committed patients to Lexington and Fort Worth who were then discharged to community centers. We then developed community facilities for examination and evaluation, which took some of the pressure off the two institutions. We then developed community-based inpatient care facilities which proved to be more economic than inpatient care at Fort Worth.

It had long been the policy of HEW to close Fort Worth and Lexington. When the budget people saw that they could implement the NARA program without the Fort Worth facility and its 300 to 400 positions, it was decided that the facility was unnecessary, and it was transferred to the Bureau of Prisons. It was then inevitable that Lexington was going to follow suit. I don't believe anyone foresaw the closing of the two hospitals when the NARA legislation was passed.

Title IV of the NARA allowed the establishment of some community treatment centers and the giving of treatment grants.

Today there are three areas in the United States that still use the NARA program. Dr. Diamond did a very nice job of explaining why New Orleans does very little for itself. Many addicts are committed through NARA and are sent to North Mountain, Ariz., for inpatient treatment and back to Tulane University for outpatient treatment with the Government paying 100 percent of the bill. Kansas City, Mo., also uses NARA. Last year I announced to Judge Oliver, of Kansas City, that we were closing NARA. He looked at me and said, "Young man, how long do you intend to spend in prison?" I said, "I don't understand, sir. I'm out here to explain to you the Federal Government policy." He said, "The trouble with this administration is that it neglects the law of the land. So long as NARA is law, I will commit under NARA. If you fail to provide me with inpatient and outpatient facilities for my civil committees, you are in contempt of this court and you are going to jail. Do you understand?" I said, "Yes, sir." And I got out of there, and we have a contract in Kansas City, Mo. I am not going to jail over this act, or any other one, if I can avoid it. A judge in Arlington, Va., also uses NARA which supports the Second Genesis facility.

Dr. Jerome H. Jaffe, *Director, Special Action Office for Drug Abuse Prevention, Executive Office of the President, 1971–73*

Reminiscences of a Drug Czar

Jerome H. Jaffe, M.D.

A little while ago Don Jasinski made the comment that "at this gathering people like Harris Isbell, Abe Wikler, and Frank Fraser are youngsters who made good." I can't help, therefore, feeling deeply honored to be counted among those invited to participate in this symposium.

Occasions such as this have a number of functions. They provide an opportunity for those of us involved in research and in the planning of research to pause, to take stock, and to look back and ask that painful question, "Has our enterprise been worth the effort, the sacrifice, and the expenditure?" They also serve the purpose of permitting us to take note of how decisions were made to pursue one research effort rather than another, one program rather than another, and to serve if you will as our own historians. I think that, to a certain extent, many of us recognize that we cannot shirk that responsibility, and I hope that Dr. Felix's comments last night were recorded and that they won't be lost to history.

In the process of recalling how decisions were made, we often find linkages that connect research, sometimes directly and more often indirectly, to decisions about national policies and programs. Yet, at the time policy is evolving the relationship is apparent only to a select few. On occasions like this, researchers are called upon to acknowledge their progeny, legitimate and illegitimate; those that have given us cause for pride, as well as any that have brought us embarrassment and shame. It is incumbent upon those who have made policy or developed programs to acknowledge those whose research generated the factual underpinnings that gave birth to such policies or programs, or in the interest of history to acknowledge that the programs were born without benefit of such parentage. In his presentation on civil commitment, Karst Besteman gave some hints about how our Government decided how long someone should be civilly committed. Other speakers have been equally candid.

As the first Director of the Special Action Office for Drug Abuse Prevention, I thought I might best serve this audience and the historians of tomorrow by tracing some of the links between the activities of the Lexington PHS Hospital and the ARC and the creation of the Special Action Office and some of the relatively recent changes in national policy. I should begin by emphasizing that my observations here can cover only a very small part of the network of relationships among people, among lines of research, and among policies. Although I will focus more on the people and research of Lexington that directly influenced me, we should all be aware that the Lexington PHS Hospital and the ARC have influenced others who have, in turn, become major influences on the development of national and international policies.

The influence of an institution takes many forms. We have already heard of the many men who were here, those who stayed, and those who went on to major administrative tasks (Kolb, Felix, Lowry, Diamond, Yolles, and Kieffer), those who did their research here (from Himmelsbach through Isbell, Fraser, Wikler, Martin, O'Donnell, and Ball), and the research itself, to which I will return later. But we should recognize that the track record of the clinical facilities also had an impact on the evolution of other programs. The relapse rate from our two Federal hospitals was such as to give almost anybody else who developed any other kind of treatment a national forum if they could claim successful rehabilitation of more than 10 percent of narcotics addicts. This situation had a major influence on the development of programs. Synanon, merely by demonstrating that addicts could exist and function without locked doors and without drugs, became a national movement. Then there were the trainees, of whom I consider myself one of the lesser, and among whom we would count Marie Nyswander, who in a variety of ways influenced Vincent Dole who, in turn, developed the methadone-maintenance concept. We need to recognize, too, the research of the affiliates, the University of Michigan with their entire group of graduates, and people like Ray Houde, whose work in analgesia was interlinked with Lexington and Michigan.

My own connections with ARC began actually more than 18 years ago when, as a medical student, I came upon Abe Wikler's review, *The Relationship of Psychiatry to Pharmacology.* Such was the encyclopedic scope of that review that to this day I am not sure that I have ever read the entire monograph. I became convinced that to learn psychopharmacology one could do no better than to seek out the man who wrote the treatise. The details of the correspondence that then took place between Professor Wikler and me are better deferred to another time. Suffice it to say, I did not succeed in obtaining a position with Dr. Wikler. I did, however, sign up for an internship with the U.S. Public Health Service, thinking, naively, that somehow the Lexington facility was just one place. I had hoped that as an officer in the PHS I would get the opportunity to work with Dr. Wikler, which I could not get as a merely interested graduate of a medical school. As my year of internship drew to a close, those interns who had Armed Service obligations still unfulfilled (at that time they were still drafting doctors) were presented with an interesting set of options. We could seek one of a number of residencies offered by the PHS Hospital system and thereby fulfill our service obligations; we could accept other service with the PHS, such as general medical service in Alaska, the Indian service in Rosebud, Tuba, or some similar center of learning; or, we could resign and seek residencies outside the PHS, in which case the friendly PHS indicated it would take all steps available to see that we were drafted directly into the Army. It was then that I learned, for the first time, about the essentially impersonal nature of bureaucracy, and that the famous Addiction Hospital at Lexington was entirely distinct administratively from the famous Addiction Research Center which was part of NIMH, even though they were both in the same building. Although a residency in psychiatry at the PHS Hospital in Lexington was very different from a research position at ARC, Dr. Wikler's book had convinced me that those who self-administered drugs could teach us a great deal about drugs and psychiatry, so I really didn't feel too disappointed about missing the opportunity to do research. But, en route to Lexington, I met a somewhat bewildered doctor who was taking his licensure exam. He aspired to be a general practitioner in the hills of Pennsylvania, and he related with considerable apprehension and disappointment that in fulfillment of this service obligation he had been assigned to work with someone named Wikler, about whom he knew nothing except that he was doing research on addicts.

I had no idea during those 2 years I spent at Lexington that the issue of drug use and drug addiction would someday become a national issue, but the experience left its imprint in more ways than one. When I finally found an opportunity to do research in psychopharmacology at Albert Einstein College of Medicine in New York, I became interested in mechanisms of physical dependence. By the early 1960's, the problem of addiction was still of interest to only a small group of researchers and, except in New York City where detoxification programs were available, the treatment options for addicts in the United States were still limited to the hospitals at Lexington and Fort Worth and to Synanon in California. Under these conditions, medical people with any experience in handling addiction were experts (the old story of one-eyed men in the land of the blind). As a local expert, it was not a big step to get involved in treatment. Half of the patients I had treated at Lexington were residents of New York, and since my phone was listed they tended to call me when they were in trouble. When Bill Martin described the properties of cyclazocine in 1965, it was immediately apparent that there might be a way to test the notion that opiate addiction involved a large component of conditioning, which is something that Abe Wikler had been saying since 1955. But the advent of cyclazocine, which was a nonnarcotic substance, was important in at least three other respects. First, it provided added momentum to the growing view that opiate addiction need not be a hopeless problem. Second, when the availability of cyclazocine was added to the availability of detoxification, therapeutic communities, and methadone, it forced us to recognize that there might be a variety of ways to modify the addiction syndrome and that we needed to know more about how to fit these approaches or "modalities" together. Third, the fact that addicts would volunteer for cyclazocine further supported the view that the stereotype of the addict as "pure psychopath" was badly in need of change. It was time to state again what Lawrence Kolb had noted in the first days of ARC: that addicts are a heterogenous group and that our society's response needs to be predicted on that heterogeneity. The idea that opiate addiction was a distinct disorder that could be superimposed on any kind of personality as a result of learning and of conditioning to environmental stimuli was a major contribution of the researchers of the ARC, a contribution that not only supported Kolb's observations about heterogeneity, but also was one which was destined in time to have a profound effect on national policies. I will say more about such policies shortly.

By 1965, I was already familiar with the Hospital at Lexington, and with Synanon and Daytop Village; I had been working with methadone on a limited scale, and then became involved with cyclazocine studies. These experiences forced me to think in terms of how the people, the theories, and the available treatments could be put together. The administrative obstacles to developing a program that could compare these approaches led me to Chicago where there was a committee, appointed by then Governor Kerner, charged with planning drug programs. I was delighted when this group was willing to consider a scheme to compare various treatment approaches. Actually, the Committee was not that interested in controlled comparisons at first. Its first thought was to follow in the footsteps of New York City and to make a massive commitment to therapeutic communities, such as Synanon. The members of the committee had never heard of cyclazocine and were rather negative about methadone, but I was able, nevertheless, to convince them that Illinois needed a "multimodality approach." Creating a structure that would accommodate what were then bitterly rivalrous groups proved to be a time-consuming task for a number of reasons. A major one was that, in Chicago, in 1967, we really could not appreciate that the country was entering the rapid growth phase of the heroin epidemic of the late 1960's and early 1970's. Very quickly it became apparent that I would have to choose between expanding the treatment capacity of the programs to take care of the increasing number of addicts seeking treatment, or continuing to focus on the research. I felt that somehow I had an ethical responsibility to respond to the needs of the treatment program. I spent the next 3 years trying to conduct some research while expanding treatment capacity.

The next phase of this story started with my first contact with the White House staff. This occurred in the spring of 1970 when Mr. Jeffrey Donfeld of the Domestic Council staff dropped in to see me in Illinois as a part of his self-education in the field of drug-addiction treatment. Mr. Donfeld had, in turn, been sent by Dr. Robert DuPont, who later told me that I had once spent several hours on the telephone with him when he was trying to set up a treatment program for the District of Columbia. I had forgotten this episode until he reminded me of it much later; this gives you an idea of the many, many telephone conversations I must have had that lasted a number of hours.

In October of 1970, I was again contacted by Mr. Donfeld, who asked me to put together a group of experts in the area of drug abuse and addiction to draft a report on the nature and causes of the current drug-abuse situation, and to make recommendations for doing something about it. His conditions were patently impossible. He wanted the committee to agree to keep the report totally confidential, to meet within the next 2 weeks, to complete a report suitable for submission to the President within 6 weeks. After extended negotiations, he offered a 2-week extension of the deadline to December 25, 1970. In retrospect, it is not clear just how it was accomplished, but a report was delivered to the White House within the time alloted. Twenty percent of the people on that committee had been associated with Lexington, (i.e., Jack O'Donnell and me); and if John Ball had agreed to participate despite the pittance of a consultant's fee that they were offering, that figure would have been 30 percent. As it was, John declined. We did have an interesting group; but that's a story for another time. The report of this ad hoc committee was not the only report on the treatment and rehabilitation aspects of drug addiction that the White House had solicited. Another report had been prepared by a committee given a similar charge, a committee made up of representatives of various Federal agencies involved in responding to the problem. After making the usual strong statements about the complexity of the problem and the need for setting priorities, both reports presented an analysis and recommendations. There was a very large degree of overlap, but there were also striking differences. The most striking differences between the two reports lay in their views about the genesis of heroin addiction and the possibilities for improving the situation. The Federal agencies' report took the view that heroin addiction was primarily a symptom not of individual pathology or drug availability, but of social alienation and despair over social and economic conditions amenable only to programs aimed at changing social and economic conditions, and to the development of alternative life styles for the alienated middle class. In addition it took the view that the availability of drugs in urban areas in the United States was a result of demand, rather than the view that availability makes possible experimentation which in turn leads to addiction. It specifically took the position that the use of methadone on a large scale was not advisable and that it would be a "simplistic response." In short, it said we couldn't do much, we needed more research and we needed to change society along most of its established dimensions. It was not a report to thrill somebody who wanted some action, but I think Mr. Besteman has made clear that there were, at the time, some institutional biases against moving toward any ambulatory use of a medication such as methadone.

The final report of the ad hoc committee of outside experts did not make sufficiently explicit its basic view that heroin addicts are a hetereogenous group, but this was largely a matter of trying to keep the report brief. Donfeld told us it had to be written in a 100 pages or less. In contrast to the "in-house" report, the report of the ad hoc committee was unequivocal in stating that there were some steps that could have some impact: e.g., for hard core heroin addicts oral methadone maintenance should be among the treatment alternatives available, and that where necessary Federal funds ought to be provided to make such treatment available as part of an overall response to heroin addiction and the crime association with it. You can imagine the name given to the report of the ad hoc committee by those who wrote the "in-house" report.

Other speakers have pointed out that at high levels in Government, even prior to the Nixon Administration, it was generally believed that somehow heroin addiction and crime were associated. The ad hoc report was quite explicit in estimating that, at best, we could expect available treatment for heroin addiction to have an impact on somewhat less than half of the active addict population, then estimated at 200,000, and that we should expect no impact on problems of nonopiate drug use.

With respect to youth culture the two reports were similar, and surprisingly the ad hoc commission's position on marihuana was considerably more explicit in suggesting legislative changes than that of the government group which are largely silent. The ad hoc report also complained about the proliferation of Federal agencies involved in treatment, education and research, the apparent waste, the apparent failure to do something about inordinately expensive programs, and the absence of, and the need for, long-term planning.

As far as I was concerned the episode was over. The ad hoc committee had completed its task. We expected that sometime in the future the role of the Division of Narcotics and Drug Abuse of NIMH would be expanded, and that the expansion would include some means to check the tendency of a dozen Federal agencies to fund programs in research according to whim or to please special constituencies rather than as part of some grand plan. We hoped that a hard nosed effort of evaluation would help to make the available funds achieve maximum impact. We also hoped that there might be a little more support for treatment programs.

As I look back on that committee effort, it strikes me as being at once naive and idealistic in the extreme. It made a number of assumptions that were of dubious validity. The first was that a rational discussion of the policy options was possible in the political arena. The second was that there was support and interest in efficiency or coordination outside the White House or the Office of Management and Budget. The third is that the mechanisms of government at the Federal level would permit the implementation of any plan that deliberately started out with a low expenditure and predicted that the expenditures would grow larger over the years. Lastly, it assumed that the White House staff wanted merely another viewpoint. It now seems apparent that the White House staff was quite aware of my view that the use of methadone could no longer be viewed as "a little experiment," but needed to be incorporated into an overall approach to reducing the social cost of heroin addiction. It may be that I was selected to articulate and give academic credibility to the conclusion the White House staffers had already reached. For the White House, committed to those actions that were feasible over the near term, the viewpoint articulated by the in-house report that we should respond to opiate use either with more research or with massive, radical social change was simply not an acceptable position. In short, the

White House had concluded that the bureaucracy was wrong and they wanted action.

What I was not aware of at the time was a "behind the scenes" movement to create some means to get that action started and to make it clear that such action was an initiative of the Nixon Administration making good on its commitment to do something about crime and drugs. It is useful to emphasize here, since even many people who are experts in the field of drug addiction are unaware of it, that in all Federal budget analyses starting from 1969, and quite likely for some years even before 1969, drug addiction problems have never been included as part of the health-care budget. From a Federal perspective, the area was designated "crime and drugs." This practice apparently began before the Nixon Administration came into being because that is how the problem was viewed by Nicholas Katzenbach when he was Attorney General. Thus, the linking of drugs and crime as a single category was by no means a recent innovation.

What no one could foresee in the closing months of 1970 were the events that were to bring the problem of drug addiction to the center of the political stage. The full force of the drug use epidemic of the late 1960's and early 1970's had begun to be felt in early 1971. It made itself manifest in long waiting lists for treatment programs, increased overdose deaths, spiraling crime rates, and in growing numbers of people arrested for drug offenses, and the number of arrestees found to be addicted to heroin. Then in April of 1971, two members of Congress, Representatives Steele and Murphy, went to Vietnam and made the frightening observation that up to "30 percent of the GI's were addicted to heroin." This, as you can understand, made headlines. From all sectors came suggestions for responding to the problem and predictions about the consequences. All of the predictions were of catastrophe, ranging from 150,000 new addicts roaming the streets armed with M-16s to 150,000 new addicts roaming the corn fields of Iowa and neat lawns of suburbia, eventually creating 1.5 million new addicts: the conventional wisdom was that every addict makes 10 new addicts. All of the suggestions for responding seemed unacceptable at the time. They ranged from civil commitment for 4½ years for all GIs using opiates to immediate surrender of the U.S. forces and withdrawal from Vietnam. The suggestion about civil commitment did not include hints as to how to persuade armed GI's to volunteer for this procedure. The suggestion about immediate withdrawal did not hint as to what we might do with all the heroin users after the surrender. This was an especially vexing problem in view of the fact that there were already more people seeking treatment than we could possibly handle.

To the public, the apparent response to these two problems—undercapacity to treat those who wanted treatment, and the impending doom on its way from Southeast Asia—was a major presidential speech on June 17, 1971 announcing the creation of a Special Action Office for Drug Abuse Prevention within the Executive Office of the President. The office would have the full backing of the President. It would make everybody work together: the Department of Defense, the Veterans' Administration, the Office of Economic Opportunity, the National Institute of Mental Health, the Food and Drug Administration, the Bureau of Narcotics and Dangerous Drugs, and a few sundry others. And who would accomplish this herculean task: the ruthless Dr. Jerome H. Jaffe, the "banger of heads," by Executive Order "czar of all the bureaucrats." There are several stories that precede this point that I cannot relate here because I want to focus on the essential story—the linkage between Lexington and this major acceleration of activity in the field. From the administration's viewpoint, the motives for this initiative should have been apparent from any analysis of its election campaigning or from a consideration of the views of the general public. At that time, pollsters were finding that when the American public was asked to rank the problems of society, the average American did not count the health and happiness of hippies and junkies among the first 500 problems. It was somewhat lower on the list. On the other hand, Americans ranked drugs affecting their kids and crime rather high up on the list. In fact, "drugs and crime" linked together was considered more urgent a problem than unemployment or inflation. If there was to be any thrust in terms of treatment it would have to be justified on the basis that while Americans didn't really care much about treating addicts, if providing treatment would make their own lives a little safer, a little less distressing, then they would be willing to pay the bill. This view was never articulated in quite so simple a way during the years that I was in the Executive Office, although I used these exact words in speeches on many occasions. The speeches that came out of the Oval Office were framed in terms of a plea for compassion for those victims of addiction along with a commitment to action against traffickers. It seemed as though the decision to provide treatment and the enthusiasm for getting the job done had, at least temporarily, persuaded the President and his staff that treatment and compassion were not unreasonable things to talk about and that the effort was probably worth while on its own merits. But there was no question that the results of the effort would be measured not only in terms of the health and happiness of the victims of addiction or of how well the addicts fared in terms of vocational adjustment, but even more by the FBI crime statistics.

At that time my friends told me I was being "set up," that when the inevitable disillusionment set in the sins of the political community would be put upon my head, and I would be sent into the wilderness. I did not doubt the correctness of the assessment. But, I thought I saw an opportunity that might not come again. It seemed to me that, regardless of the motives that lay behind the decision to give treatment, research and prevention status and resources comparable to those given previously only to law enforcement, unless the President could see this effort as his initiative and his program rather than that of his political opposition, the effort would not elicit his enthusiasm and his attention. And without these, the possibilities for substantial changes in national policy were small. At the time, I felt that even with a Presidential commitment, the options for change were limited. With a 75-year history of prohibition of opiates, there was no likelihood whatsoever that this country would adopt policies making intravenous heroin (or any narcotic) available on demand to all and sundry. Undoubtedly this country would continue to prohibit the recreational use of opiates, and based on past experience, in the absence of major changes within the criminal justice system, there would continue to be illicit opiate traffic and high prices for those who seek to use such drugs for recreational purposes. I felt that 45 years of research had taught us that, given such a situation society's responses were wrong on both extremes. On one extreme the picture of the psychopathic, incurable, unredeemable, untrustworthy addict inevitably involved with crime was an erroneous stereotype. On the other extreme, as Mr. Besteman clearly described in his presentation at this symposium, in terms of some judges, in some cities, there was an equally erroneous stereotype that the addict was an average good fellow who was merely unfortunate in his family's choice of neighborhood and who, if not for his addiction and/or the high price of opiates, would have been an upright citizen-taxpayer just like you and me. The first stereotype led to situations where even if an opiate addict did want to function as a law-abiding citizen, he or she was treated, nevertheless, as a pariah. These public attitudes precluded the possibility of an opiate user obtaining legitimate satisfaction from society, and contributed to the high relapse rate. Such addicts usually wound up serving long jail sentences for possession, or sale of drugs, or theft. The second and equally inappropriate stereotype arose in part as a reaction to the first and had its main impact on the courts. The effects reached the point where, in some cities, addicts who committed crimes, even repeatedly, were able to portray themselves as helpless victims of an irrational society. As a result, they often received minimal penalties for major and/or repetitive offenses.

The decision to create the Special Action Office opened up possibilities that had not even occurred to those of us who were on the ad hoc committee. It became possible to aim at changing social attitudes toward addiction and toward the addict in a direction more in keeping with our understanding of the complexities of the syndrome and the heterogeneity of those who are affected. My strategy for achieving this change was expressed in a phrase that I hoped would be acceptable to both a law-and-order administration and to a humanistic, treatment-and-rehabilitation community. We would "create a surplus of treatment capacity" and develop administrative devices that would stimulate programs to seek out the users and the addict and bring them into treatment. The objective was to create "a condition where no addict could say he committed crimes to get drugs because he could not get treatment." The hope was, on one hand, to permit the courts to protect the public by responding more appropriately to the repetitive, criminally oriented offender who happens to use opiates, and on the other hand to convey the message with the expansion of treatment programs that opiate dependence is not a hopeless situation and that in many cases the opiate user, whether maintained on a synthetic opiate or detoxified, could make a contribution as a law-abiding productive citizen. In the process, changes in public attitude would give the drug user access to more conventional rewards of society and would thereby decrease the likelihood of relapse. There are some who insisted on labeling this expansion of treatment as "a massive methadone program." If it was, that was not the specific intent. The intent was to follow through on the original observations of Lawrence Kolb and a succession of careful observers at Lexington who noted that at least a substantial proportion of opiate addicts could function well on controlled doses of opiates. It was to permit opiate addicts to decide for themselves if they wanted a therapeutic trial of controlled dependence on an opioid simply by making such treatment available along with equal availability of other nonmaintenance approaches. The notion of a variety of approaches that might best be suited to different types of addicts or to the same addict at different points in his or her career was the central theme; i.e., the multimodality approach. It was a theme which incidentally I presented first in 1966 at a CINP conference to which I was invited by Abraham Wikler.

The price tag in dollars for creating this multimodality treatment surplus was not a trifling amount. In round numbers, it was about a quarter of a billion dollars a year. Although this amount may not be great when compared to the amounts that some of our statesmen promise sovereign foreign nations to facilitate political dialogue, to obtain a commitment to such spending at a time when other medical and social problems were being curtailed was an incredible achievement. Initially it was my view that whether or not the network of treatment programs had major impact on the majority of addicts, it would accomplish several important objectives: (1) it would affect public attitudes and would probably provide some door out of an otherwise miserable life for some addicts; (2) it would also give us a better way to estimate the number and variety of drug users because we could collect data from the network of treatment programs; and (3) it was probable that we would also be able to develop some clinical populations near universities so that we could engage the intellectual powers of the universities across the country. Without question, compared to the situation of the 1950's and 1960's, this expansion of treatment availability was equivalent to a radical modification of the American response to opiate addiction. Whether this effort will achieve objectives that are viewed as worth the effort or whether we will begin to look back at the situation that existed prior to the creation of the Special Action Office in 1971 as a more desirable situation, remains to be seen.

Most observers do not entirely appreciate the direct linkage between the work of ARC and these dramatic alterations in national policies. I promised Abe Wikler I would try to tell the story of this linkage and of the events that intervened between the period in the spring of 1971 and the creation of SAODAP with its large budgetary commitment early that summer. I don't have time to relate all the details, but the essential features are as follows.

When the seriousness of the heroin problem in Vietnam became clear in the spring of 1971, the White House requested some ideas from the various government agencies about what they were going to do about the problem. As far as I can tell, they elicited the typical bureaucratic response. First, that there was no problem akin to what those Congressmen were describing. Second, that there was nothing that could be done. Third, the responsible agencies were already taking all steps that were possible.

I got involved in structuring the eventual Federal response to this problem even before the Special Action Office was created, and it is my belief that it was the way in which that response was developed which led to the creation of SAODAP several weeks later. The new approach to the Vietnam drug problem made radical changes in the way the military had traditionally responded to illicit drug use. The impetus behind these changes began when Mr. Donfeld again called me in late May of 1971 and asked if I could come to Washington on May 30th to discuss some problems. When I arrived he told me about the situation in Vietnam: the 30 percent estimated addiction rate, the 12,000 miles between Vietnam and the nearest treatment facilities, the viewpoints of the Department of Defense, and the fact that each day 1,000 men were boarding planes for the United States where the majority were discharged to civilian life within a few days.

My own response as to what ought to be done had to be based on theory, since there was no precedent for the situation. First, I felt that most of those who were thought to be addicts were probably more appropriately viewed as users, who would probably do well after their return to the United States where the availability of the drug would be considerably lower. But I also reasoned that among those who were addicts after return, we could expect the relapse rate to be lowest if we prevented them from experiencing withdrawal in their home environments. That is, if conditioning of withdrawal phenomena takes place, it would be preferable to have such phenomena conditioned to an exotic environment (Vietnam) that the users are not likely to encounter after discharge. We could also expect that, to the extent that prolonged heroin use and physical dependence lead to protracted abstinence, the sooner we are able to interrupt the opiate use and the longer the period we can interpose between the last use in the military and the first exposure to opiates in civilian life, the lower the probability that opiate use will be reinitiated in civilian life.

In addition, it seemed reasonable to postulate that many of these men were using opiates because the drugs were readily available, because heroin use had become so acceptable that there was actually peer pressure to participate in use, and because there was not a credible deterrent. It followed that if we could identify users before they became addicted and isolate them briefly, we could simultaneously interrupt the development of the addictive process and remove one element in the contagion process and, by not providing credit toward rotation out of Vietnam for the period of isolation, we could create a moderate but credible deterrent to use.

In short, what we had to do was to prevent continued heroin use by those already using it but not physically dependent, get those already addicted to detoxify *in Vietnam*, and to stop the spread of heroin use among peer groups.

My approach to this was to suggest that we test the urine of every serviceman departing from Vietnam, and invite those with urine positive for opiates to sojourn with the military in Vietnam for yet a few more weeks. After this initial phase of the program was established we would test those not scheduled for immediate departure. One small problem was the Uniform Code of Military Justice under which use of illicit drugs was a court-martial offense. To me, to compel men to submit to a test that could result in criminal prosecution would violate the Constitution as I understood it. The solution to this problem was a terse memo from the President to the Secretary of Defense. It covered four major points:

(1) Effective immediately, drug use *per se* was not to be a court-martial offense.

(2) Effective immediately, the Department of Defense was to undertake a program to identify active drug users and addicts.

(3) Such users would be offered treatment.

(4) Addicted servicemen were to remain in treatment for 30 days before discharge to civilian status.

This major change in the military approach to drug dependence was initiated the same day the Special Action Office was established and will probably be viewed in retrospect as one of its more important accomplishments. The planning and implementation of this new approach took place in some rather hectic times of 24-hour work days over a 2½-week period, and the effort had an important impact on key members of the White House staff by demonstrating that it was possible to initiate systems in the area of treatment and rehabilitation with some efficiency. The impact of the plan was probably the basis for SAODAP's initial leverage within government that in turn made a number of major changes in treatment and research possible. Certainly it provided the leverage for the funding that has permitted the kind of commitment to research that now exists.

In retrospect, some of the achievements of those first 2 years probably came about because I was too ignorant or too stubborn to realize that anything was impossible. While I am on the subject, I want to point out that accomplishing some of the things that we set out to do after the office was created would probably have been impossible except for the cooperation of one man at the National Institute of Mental Health who was equally unable to recognize the impossible. He, too, was a Lexington alumnus. I never told him this, but whenever Karst Besteman came into my office I could not help thinking that to a large degree, the Federal Government's effort to build a new and better system was dependent on this one man. I don't think that Karst has ever received sufficient recognition for his tremendous accomplishments over those hectic years.

Just yesterday, the headlines of the Washington newspapers were again shouting that the Nation's narcotic problem is worse now than it was 2 years ago. It would seem that we still have a long way to go before we will be able to have a dispassionate and rational dialogue about the problem of opiate addiction. If that day ever comes, it is likely that the rational part will be built on the solid foundation of the research that has been done by the pioneers of Lexington, the collective wisdom of those who passed through its doors, and those who came directly under its influence.

Dr. Everette L. May, *Chief, Section on Medicinal Chemistry, National Institutes of Health*

Role of the National Research Council, National Academy of Sciences, in the Opiate Problem, 1929–75

Everette L. May, Ph.D.

The Committee on Problems of Drug Dependence, as we now know it, was spawned as the Committee on Drug Addiction early in 1929 when Dr. William Charles White was still Director of the Division of Medical Sciences, National Research Council. Its first meeting was January 12, 1929. This Committee, unchanged except for the addition of two members, served until 1939. In May of 1929, the Committee decided to develop a chemical-pharmacological-clinical research plan.

About this time, Dr. Lyndon Small, with Ph.D. training from Harvard, a brilliant alkaloid chemist and Assistant Professor of Research Chemistry at the University of Virginia, had just returned from 2 years' work with Dr. Heinrich Wieland of Munich, Germany. He accepted the directorship of the chemical effort (called the Drug Addiction Laboratory) and space was supplied by the Cobb Chemical Laboratory at the University of Virginia. Funds, at first not to exceed $50,000 per year were from a 10-year Rockefeller grant. Dr. Small and a few graduate students were to be concerned with modification of the main phenanthrene alkaloids occurring in opium—morphine, codeine, and thebaine. A program involving total synthesis of partial or simulated structures of morphine was to be directed by Dr. Erich Mosettig from Professor Ernst Spaeth's laboratory in Vienna.

Nearly a year later (June 1930) when the need for pharmacological examination became pressing, Dr. Nathan B. Eddy, who had been teaching physiology and pharmacology at the University of Alberta, Edmonton, was appointed to head such a pharmacology program at the University of Michigan in Dr. Edmund's laboratory. It is not quite clear from Dr. Eddy's account just why Michigan was chosen as the site for these investigations, but during part of the preceding 2 years he had worked in the laboratory of Dr. Robert Gesell at the University of Michigan. In any event, Dr. Eddy came to Ann Arbor, June 1, 1930, and was given the title of Research Professor of Pharmacology with the academic rank of Associate Professor. Dr. Eddy, in addition to initiating baseline studies for morphine and codeine, served in a liaison role by visits to the University of Virginia and other centers of activity in the committee's interest. I had the good fortune to become a miniscule part of this program about 1935 when I enrolled in the Graduate School of Chemistry at Virginia and was accepted into Dr. Small's laboratory with Dr. Mosettig as my mentor.

During 1929–39, at least 200 new compounds were prepared and evaluated. The more promising ones which were deemed safe for man were studied by Dr. Himmelsbach here at the Addiction Research Center. And, although this effort was not productive of practical results, a fair amount of good basic chemistry evolved along with solid pharmacology and structure-activity data. These are well documented in all three editions of Alfred Burger's Medicinal Chemistry and a publication to be mentioned below. In addition to many journal publications compiled in the National Research Council Report of the Committee on Drug Addiction, 1929–41, Supplement No. 138 to The Public Health Reports entitled, "Studies on drug addiction," appeared in 1938—authors, Small, Eddy, Mosettig, and Himmelsbach.

The last full meeting of the Committee on Drug Addiction was held January 28, 1939, but it was agreed that (as a Division of Medical Sciences Committee) it would continue in an advisory capacity. On June 27 of the same year, Drs. Eddy and Small were jointly the recipients of the first Scientific Award of the American Pharmaceutical Manufacturers Association, presented by the Honorable Harry J. Anslinger. Dr. Eddy, in his acceptance remarks, noted that the award was an important recognition of the coordinated research sponsored by the Committee.

It was in June of 1938 that plans for transfer of the Virginia program to the National Institute (later to become Institutes) of Health (to continue the research of the Committee on Drug Addiction in close association with the PHS Hospital at Lexington) began to take shape. This, according to Dr. Eddy's account, was mainly through the interest and efforts of PHS Surgeon General Thomas Parran, and Dr. Ross Harrison, Chairman of the NRC (but Dr. Isbell tells me that Drs. Lawrence Kolb, Sr. and Walter Treadway were probably more influential in this respect). So, at the close of business at Virginia about mid-1939, Small, Eddy, and Mosettig moved to Washington, D.C., to resume their studies under Government auspices with, as stated before, the Committee on Drug Addiction serving in an advisory capacity.

With the intervention of World War II and deep involvement of the United States late in 1941, malaria became a defense problem, so that efforts during the next 5 years were almost entirely devoted to this project. Nevertheless, Dr. Eddy, with collaborators Sumwalt and Krueger, was able to complete (1941) another PHS supplement on the "Pharmacology of the opium alkaloids." In addition, with Dr. Small and representatives from the pharmaceutical industry, the Bureau of Narcotics, the Public Health Service, and the Narcotics Advisory Committee, Dr. Eddy made arrangements for the manufacture, distribution, and further clinical testing of metopon, a morphine relative which had been synthesized by Dr. Small and associates at Virginia.

In the meantime, some exciting reports were emanating from Germany, the discovery of new, totally synthetic analgesics, pethidine, (meperidine, Demerol, 1939) and methadone (1945) and congeners. Methadone received especial attention because of its close pharmacologic similarity to morphine and a possible opium shortage. Consequently Dr. Weed, Chief of the Division of Medical Sciences, NRC, at that time formed a (new) "Committee on Drug Addiction and Narcotics" (about 1947), one of 15 medical advisory committees of NRC, "to deal with present and future problems relating to synthetic narcotics and drug addiction." The membership of the Committee included Dr. Isaac Starr as chairman; Dr. Eddy, Secretary; Mr. Anslinger and Drs. Raymond Bieter, Dale Cameron, Walter Palmer, Maurice Seevers, and Lyndon Small. Dr. Starr and Dr. Eddy continued in these positions until 1960. The first meeting of the Committee was held October 2, 1947 at the NAS Building, Washington, D.C., with liaison representatives from the Office of the Surgeon General of the Army, the Bureau of Medicine of the Navy, the Naval Medical Research Institute, the Food and Drug Administration, the American Medical Association, and the American

Drug Manufacturers Association attending. This liaison relationship has continued throughout the years, and the Committee has constantly advised on new chemical types of analgesics and congeners.

With cessation of the malaria program, Dr. Eddy began a mass testing program for analgesics, refined the Wolfe-MacDonald hotplate method of testing, and, I believe, began rather informally (at NIH) the coordination part of the NRC drug-dependence program that has persisted to this day. Dr. Mosettig and I resumed our research in this area with operations on the methadone and isomethadone molecules and at length prepared all the possible methadols, isomethadols and their O-acetyl derivatives, some 24 compounds in all. All of these were tested both subcutaneously and orally in the hotplate method and for acute toxicity. One of these has become popular as LAAM, *levo*-alpha-acetylmethadol, as most of you know. Dr. Small and his associates went back to transformations of the morphine, codeine, thebaine, and neopine molecules and continued this until his death in June, 1957.

About 1952, we began our research on the phenylmorphans and benzomorphans, which ultimately led to phenazocine, metazocine, and indirectly to pentazocine and cyclazocine. Other chemical and biomedical areas have been and are still being pursued in our laboratory but not with any major thrust.

Time will not permit me to give the genesis of the research fund, the grants program, and the establishment of Dr. Seevers' dependence studies in monkeys at Michigan. This is all well detailed in Dr. Eddy's book which he finished just before he died in 1973. "The National Research Council Involvement in the Opiate Problem, 1928–71." Suffice it to say that the (worldwide) pharmaceutical industry has supplied most of the (fluid) funds with, however, substantial supplemental help by various government agencies, particularly the National Institute of Mental Health (now NIDA). Eventually, Dr. Seevers' facility included a Beagle-dog colony for assessing barbiturate dependence. The program has grown steadily and there has been good coordination of effort among the National Institutes of Health, the University of Michigan, and now the Medical College of Virginia, the Addiction Research Center, the Veterans' Administration and the various grantees, all under the NRC–NAS umbrella. Nearly 9,000 compounds have been examined at the National Institutes of Health; about 1,000 of these have found their way to Michigan and 100 to the Addiction Research Center. A paltry few of these were introduced into medical practice. Thus, it is apparent that the scientific progeny of the chemist suffer a high infant mortality rate.

Now I think I should conclude with the remainder of the historical account of the committee. Dr. Eddy retired from NIH in August, 1960 but continued as coordinator of the evaluation program as an NIH consultant. He also succeeded Dr. Isaac Starr as Chairman of the Committee in 1961 and was in turn succeeded by Dr. Dale Cameron in 1962 at which time Dr. Eddy became Executive Secretary. About the same time I became a member of the Committee and succeeded Dr. Eddy as coordinator at NIH in 1965. Furthermore, on July 1, 1965, the name of the NRC Committee was officially changed to Committee on Problems of Drug Dependence to indicate an awareness of the different types of drug abuse. According to Dr. Eddy's account, the initial suggestion for such a change came from a paper written by Dr. Isbell in which he used such terms as pharmacopsychosis, morphinism, cocainism, etc. In 1967, Dr. Cameron, who resigned as Chairman to join the World Health Organization in Geneva, was succeeded by Dr. Henry Brill.

Dr. Eddy resigned as Executive Secretary also in 1967, continued as a member until 1970 and became its Chairman for a second time, 1970–71. He remained as a consultant until his death in 1973. Of him it could truly be said, in the words of the poet Tennyson: "To strive, to seek, to find, and not to yield."

As I'm sure all of you know, Dr. Frank Fraser served as Chairman from 1971–72 and the present Chairman is Dr. Leo Hollister. Mr. Duke Trexler, an employee of the NRC–NAS, has been Executive Secretary since 1969.

Over the years, this NRC Committee has served in an advisory capacity to the Food and Drug Administration, the Drug Enforcement Administration (formerly Bureau of Narcotics), and many of its members have been advisors to the World Health Organization. Among these was Dr. Eddy who, in fact, was a member of every Expert Committee on Drugs Liable To Cause Addiction convened by the World Health Organization during his lifetime. The Committee has also coauthored with the American Medical Association, several "position" papers on such important matters as "Methadone maintenance," "Use of opiates in clinical practice," etc. Finally, it has continued to give advice to the Departments of Defense and State on replaceability of the naturally occurring opiates and their transformation products by analgesics and antitussives obtained by total synthesis. Let it be hoped that the NAS–NRC will continue to look with favor on and sponsor this, the oldest, "standing" committee of its long and illustrious history.

Dr. Dale C. Cameron, *Superintendent, Saint Elizabeth's Hospital, Washington, D.C., 1962–67; Senior Medical Officer (Drug Dependence and Alcoholism), World Health Organization, 1967–74*

World Health Organization and Drug Dependence

Dale C. Cameron, M.D., M.P.H.

At the very outset, let me express my great satisfaction, both professional and personal, at being afforded the opportunity to participate in this remarkable symposium on drug dependence. The location here at Lexington, where so much pioneering work has been and is being carried out, and the presence of so many of the pioneers, other valued colleagues and long-time friends, lends the occasion a very special significance.

The organizers of this symposium have invited me to discuss the World Health Organization and drug dependence. To do so, I must stress that the broad purpose of WHO's program in this field is *to help reduce the seriousness and extent of the individual, public health, and social* *problems associated with the use of psychoactive, dependence-producing drugs outside of accepted medical practice* and not alone, or even necessarily, to prevent all nonmedical drug use per se. The latter is but one, although very important, approach that may be utilized with respect to certain drugs (e.g., heroin and some central nervous system stimulants). Such an approach, however, is not very realistic in many countries insofar as beverage alcohol is concerned. The same may be said with respect to the use of certain cannabis preparations in a number of countries. The problems associated with a person's experimental, casual, or dependent use of dependence-producing drugs are not viewed as "drug problems," as they are so frequently characterized, but as "human problems" ([3] p. 10)—drug related to be sure. So are the problems associated with providing preventive, therapeutic, and control services in the field.

Such human problems are not easy to tackle. They are probably older than recorded history and, in more recent times at least, they have been hedged about with emotion, for one thing, because they concern groups and concepts that most societies take very seriously: youth, morals, religion, and the law [5]. There is a remarkable tendency for many persons to take polar views, to misinterpret the views of others, to selectively attend to information supporting their own preconceptions, and to be less influenced by available scientific data than by their underlying beliefs about the causes and consequences of drug use and their basic attitudes towards the relative importance of individual rights and responsibilities *versus* those of society. Despite all this, it appears to me that many people concerned with problems in this field are beginning to take an increasingly balanced and less anxious view of drug-taking behavior. One perhaps now hears a good deal less about "fighting the evils of drug addiction and abuse," or "fighting the evils of drink," and a bit more about trying to reduce the extent and seriousness of problems associated with the use of alcohol and other dependence-producing drugs. Associated with this increasingly accepted perception of broad purpose, there has been a growing tendency to distinguish between problems that are primarily related to man-drug interactions (e.g., intoxication, cirrhosis of the liver) and man-society interactions stemming from the drug taker's involvement in socially unacceptable behavior (e.g., expulsion from school, loss of job, imprisonment).

As noted, the broad purpose of "problem reduction" underlies WHO's program, as do a number of assumptions or models having to do with the nonmedical use of drugs. Before mentioning those assumptions and describing some of the Organization's current activities in the field, let me recall briefly the role WHO has played in this field during the past 25 years.

Historical Background

Since its inception, WHO has been concerned with problems related to the use of dependence-producing drugs outside accepted medical practice. "Because of its obligations under various international instruments for narcotics control, it is understandable that much of the Organization's early work in this field concentrated on the drugs themselves, particular attention being paid to the identification of addiction-producing drugs (as they were then termed) and the chemical modification of narcotic analgesics with a view to developing effective and potent analgesics free from liability to produce drug dependence.

"From the very outset, WHO expert committees on the subject called attention to the fact that certain psychoactive drugs not under international control might be, or already were, subject to abuse. In November 1946, the Interim Commission of the World Health Organization decided to appoint an Expert Committee on Narcotic Drugs. Its title was subsequently changed to the 'Expert Committee on Habit-Forming Drugs,' as it was felt that certain substances, although not narcotic, should be considered by the Committee because of their habit-forming tendency. The possibility of amphetamine abuse was noted in 1949, and in 1950 it was observed that barbiturates were capable of producing 'addiction.' By 1963, the hallucinogens had also come to be considered as a problem." ([2] p. 8)

Under various instruments for the international control of narcotic drugs, WHO either makes decisions as to the need for and level of control of specified drugs (e.g., as provided in the 1931 Convention)[1] or makes findings upon which the United Nations Commission on Narcotic Drugs "may, in accordance with the recommendation of the World Health Organization," [2] make decisions on these matters. When the Convention on Psychotropic Substances [3] comes into force, WHO will be required to make findings, assessments and recommendations concerning notified drugs, but the UN Commission's decisions need not necessarily be in accord with WHO's recommendations, although the latter's "assessments shall be determinative as to medical and scientific matters."

During the last several years, without decreasing its attention to dependence-producing drugs, WHO has given increasing attention to the drug taker, to the broad and immediate environment in which he lives and to the interaction of these three major elements involved in the nonmedical use of drugs. Because of this trend, and a shift away from the use of the much-misunderstood terms "addiction" and "habituation," the names given to WHO Expert Committees in this field have gone through the following changes: Expert Committee on Habit-Forming Drugs (1949); . . . on Drugs Liable To Produce Addiction (1950–55); . . . on Addiction-Producing Drugs (1956–64); . . . on Dependence-Producing Drugs (1965–66); and . . . on Drug Dependence (1969–).

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[1] Convention for limiting the manufacture and regulating the distribution of narcotic drugs, signed at Geneva on July 13, 1931, as amended by the Protocol signed at Lake Success, N.Y., on December 11, 1946.

[2] Single Convention on Narcotic Drugs, signed at New York on March 30, 1961.

[3] Signed at Vienna on February 21, 1971.

Through the years WHO has (a) provided consultation, on request of governments, concerning the improvement of preventive, therapeutic, rehabilitative, and research programs in the field, (b) convened groups of experts to address themselves to a variety of drug-related major questions and topics,[4] and (c) given technical and some limited financial assistance in the field of training and research.

The four World Health Assemblies meeting annually in 1970 through 1973 gave major attention to the ways in which WHO might contribute to the prevention and control of problems associated with the nonmedical use of dependence-producing drugs and stressed the need for WHO to encourage and assist the development of improved programs for prevention, treatment including rehabilitation, training and research. These assemblies also emphasized the importance of developing means for the international collection and exchange of data on the prevalence and incidence of drug dependence and the associated personal and environmental factors.

In March 1971 a United Nations Fund for Drug Abuse Control (UNFDAC) was established to develop short-term and long-term plans and programs for concerted and simultaneous action on the supply of drugs for purposes of abuse, on the demand for such purposes and on the illicit traffic which serves as a channel connecting production with demand, and to provide assistance in the execution of those plans and programs. [5] That Fund now has at its disposal approximately US $16 million, most of which has already been committed. Significant support has been given by the Fund to a number of WHO activities in the field, about which I shall comment later.

Some Program-Planning Assumptions

Before turning to a brief description of recent WHO program activities, it will perhaps be useful to note some of the assumptions and models upon which they are based.

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[4] For example, references: 7, 8, 15 and 16 on alcoholism; 9 and 10 on the classification of drugs by level of control required; 11, 14 and 21 concerning principles of management of drug dependence problems; 12 on epidemiology; 13 on prevention; 17 on the detection of drugs in body fluids; 18 on evaluating dependence-producing drugs; 19 on the use of cannabis; 20 on opiates and their alternatives for pain and cough relief; and 22 on youth and drugs.

[5] Aide-Memoire accompanying March 26, 1971, letter from the Secretary-General to governments concerning the United Nations Fund for Drug Abuse Control.

Underlying the models to be mentioned is the assumption that the causes and consequences of drug taking are multiple. Any associated problems involve an interaction of the pharmacological properties of the drug(s) taken, the characteristics of those who take them, and the broad and immediate sociocultural environment in which the drug taking occurs.

Additionally, one model sees drug-using behavior as a communicable phenomenon [1]. Initial interest in trying various dependence-producing drugs often appears to be communicated directly or indirectly from a user to a nonuser. Peer groups seem to be especially important in this connection. Interest may also be stimulated by mass media accounts of events related to drug taking, particularly when those accounts are of a dramatic nature. This also applies to some well-intentioned, but ill-conceived, drug-information programs. Preventive programs need to take account of these modes of transmission of interest in drug use. Account must also be taken of the fact "that in most countries the majority of drug users take the initiative (directly or indirectly) in connection with their initial drug experience—i.e., they tend to seek the experience." ([22,] p. 22)

Another model borrows from the economics of "supply" and "demand." It holds that where there is a substantial demand for a product, someone will undertake to supply it at a price. This leads to the less apparent corollary that if one wishes to reduce the severity and extent of problems associated with the nonmedical use of certain drugs, it is imperative that a balanced approach be taken to the *simultaneous reduction of both the supply of and demand for* drugs. If we have learned anything from past endeavors in this field, it is that measures taken to limit markedly the availability of dependence-producing drugs without comparable effort to reduce demand through treatment, educational and other approaches are not likely to be crowned with notable success. The reverse is also probably equally true, i.e., to try to reduce demand for a wanted product in the face of a ready supply is not likely to be an easy task. Indeed, there probably are few easy solutions to complex problems, much as we might wish this were so.

Still another model sees drug taking—at least initial drug taking—as "functional." In other words, it appears to be an attempt to satisfy or fulfill some conscious or unconscious need or purpose of the drug taker.

> One or more of the following motives often appear to be associated with the initiation and continuation of drug taking: (1) to satisfy curiosity, about drug effects; (2) to achieve a sense of belonging, to be "accepted" by others; (3) to express independence and sometimes hostility; (4) to have pleasurable, new, thrilling or

> dangerous experiences; (5) to gain an improved "understanding" or "creativity"; (6) to foster a sense of ease or relaxation; and (7) to escape from something.
>
> It must be noted that these motives are not necessarily associated with individual psychopathology or with adverse social influences. They can be and are operational for normal as well as abnormal persons, whether or not such persons are satisfied with the social structure and situation in which they find themselves. Further, these motives do not necessarily lead to drug taking. Indeed, they can and do lead most persons to obtain satisfactions through activities other than drug taking. ([22] p. 18)

These needs, and others, "vary in intensity with different persons and within the same person at different times. Ordinarily, they require not only satisfaction at one time, but repeated satisfaction through time. It is to fulfill such needs that much drug taking appears to be initiated, continued, and stopped. It is around the satisfaction of such needs that peer groups are formed, and it is also around their satisfaction that meaningful alternatives to destructive drug taking behavior have been and can be developed." ([13] p. 57)

Some Recent Program Activities

In response to the request of the 23d World Health Assembly that the Director-General "develop means for the international collection and exchange of data on the prevalence and incidence of drug dependence, and on the human and environmental factors associated therewith" (4, Resolution WHA 23.42), and with financial support from UNFDAC, WHO is developing a research and reporting program on the epidemiology of drug dependence. This has three main components, the first of which is a system for collaborative reporting by selected institutions and members of WHO Expert Advisory Panels, to provide, on a regular basis, relatively brief factual and interpretive reviews based on *already available data* relevant to drug-related human problems in various geographic areas. These reviews are expected to contain: (a) published objective data or informed opinion on the prevalence and incidence of drug dependence of various types; (b) morbidity and mortality associated with drug taking; (c) the character and extent of available treatment, rehabilitative and preventive services; (d) the nature of sociocultural and other environmental factors that appear to be associated with drug-taking behavior; and (e) the nature of policy changes relative to drug taking and the manner of implementing these changes.

The second aspect of the program has to do with stimulating needed new research and improving the research and training resources in the field. To this end, WHO proposes, with the concurrence of the centers involved, to designate a limited number of institutions as WHO Drug Dependence Research and Training Centers. These are to be of two types, viz: (a) those that already have well-developed programs in this field, and (b) those that have the capability of developing such activities but have carried out little or no work in this field, and are located in areas with substantial existing or potential problems associated with the nonmedical use of dependence-producing drugs. The Organization hopes to foster not only bilateral arrangements between pairs of established and developing centers for purposes of staff exchange and other forms of mutual assistance, but also collaborative research undertakings involving a number of institutions.

The third facet of this program has to do with drug dependence epidemiological planning and monitoring activities designed to help develop comparable approaches for epidemiological studies of drug dependence in different sociocultural settings and to monitor changing patterns of drug use in selected high-drug-use localities. Only through the incorporation of shared elements of approach, methodology and definitions in such studies can valid comparisons between studies be contemplated.

Among other activities in which the Organization is involved are the following: (a) the operation of UNFDAC-supported treatment and rehabilitation projects in Thailand and Pakistan. These are part of larger programs that look also to the replacement of opium cultivation with other means of making a living among Hill-tribe peoples; (b) studies of the effectiveness of maintenance in the treatment of narcotic-dependent persons; (c) studies of the effects in man of the use of cannabis preparations, taking account of the amount, frequency, duration of use, and route of administration; and (d) the preparation of manuals on drug dependence for health and related personnel. The first of these was published this year [3] and will be available in Arabic, English, French, and Spanish.

Finally, let me note that, in most countries, the number of adults experiencing serious adverse effects from problem-related use of beverage alcohol probably far exceeds the total number of persons of all ages similarly affected by their use of less socially approved drugs. For this reason, WHO plans to increase substantially its work in this field. This is not to say that the Organization has not previously given attention to these problems; it has,[6] but the extent of that attention has not been commensurate with the seriousness of the public health and social problems involved.

It is hoped this account of the broad purposes, underlying assumptions, and evolving activities of WHO in the field of drug dependence has been of some interest. In closing, may I acknowledge the significant contributions that many of you present have made, directly and indirectly, to WHO's technical reports and the evolution of its activities. I wish, also, to invite special attention to the many direct services rendered to the Organization by the late Dr. Nathan B. Eddy, and indirect contributions made by the late Dr. Lawrence Kolb. WHO, like many of us here, is in their debt. Finally, may I extend my very warm thanks to the organizers of this symposium for the opportunity to participate.

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[6] For example, references 7, 8, 14, 15, and 16.

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